The American Journal of Medicine

EDITORIAL BOARD

The American Journal of Medicine

Editor ALEXANDER B. GUTMAN, M.D.
Professor of Medicine
COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK
DIRECTOR OF MEDICINE, THE MOUNT SINAI HOSPITAL, NEW YORK

ADVISORY BOARD

DAVID P. BARR, M.D.
Professor of Medicine
CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK

ARTHUR L. BLOOMFIELD, M.D.
Professor of Medicine, School of Medicine
STANFORD UNIVERSITY, SAN FRANCISCO

EUGENE A. STEAD, JR., M.D.
Professor of Medicine, School of Medicine
DUKE UNIVERSITY, DURHAM

JOSEPH T. WEARN, M.D.
Professor of Medicine, School of Medicine
WESTERN RESERVE UNIVERSITY, CLEVELAND

ASSOCIATE EDITORS

PAUL B. BEESON, M.D., *New Haven*
HERRMAN L. BLUMGART, M.D., *Boston*
EUGENE B. FERRIS, JR., M.D., *Atlanta*
HARRY GOLD, M.D., *New York*
A. MCGEHEE HARVEY, M.D., *Baltimore*
GEORGE H. HOUCK, M.D., *Palo Alto*
CHESTER S. KEEFER, M.D., *Boston*
WILLIAM S. MCCANN, M.D., *Rochester, N. Y.*
GEORGE R. MENEELY, M.D., *Nashville*
CARL V. MOORE, M.D., *St. Louis*
WALTER L. PALMER, M.D., *Chicago*
DEWITT STETTEN, JR., M.D., *Bethesda*
GEORGE W. THORN, M.D., *Boston*
WILLIAM S. TILLETT, M.D., *New York*
ROY H. TURNER, M.D., *New Orleans*
M. M. WINTROBE, M.D., *Salt Lake City*
JOHN B. YOUMANS, M.D., *Nashville*

The American Journal of Medicine is published monthly by The American Journal of Medicine, Inc., 49 West 45th Street, New York 36, N. Y. Yearly Subscription, $12.00 *U. S. A.;* $13.00 *Canada;* $15.00 *Foreign, including Latin-American countries, Single Numbers* $2.00*; Symposia Numbers* $4.00. *Entered as Second Class Matter June* 28, 1946, *at the Post Office, New York, N. Y., and on June* 28, 1946, *at York, Pa., under the act of March* 3, 1879. *June,* 1956—*Volume* XX, *No.* 6. *Copyright* © 1956, *by The American Journal of Medicine, Inc.*

MANUSCRIPTS: All manuscripts should be addressed to the Editorial Office of the Journal, 49 West 45th St., New York 36, N. Y. *Style for bibliography:* Doe, J. J. Treatment of hypertension. Am. J. Med., 6: 72, 1948.

Change of address must reach us one month preceding month of issue.

ADVERTISING REPRESENTATIVES

New York: P. A. Porter, P. D. Brewer, H. Douglas Robinson—JUDSON 2-3090
Chicago: R. H. Andrew—FRANKLIN 2-3861
Pasadena: Ren Averill—RYAN 1-9291

invitation to asthma?

not necessarily . . .

Tedral, taken at the first sign of attack, often forestalls severe symptoms.

relief in minutes . . . Tedral brings symptomatic relief in a matter of minutes. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

for 4 full hours . . . Tedral maintains more normal respiration for a sustained period—not just a momentary pause in the attack.

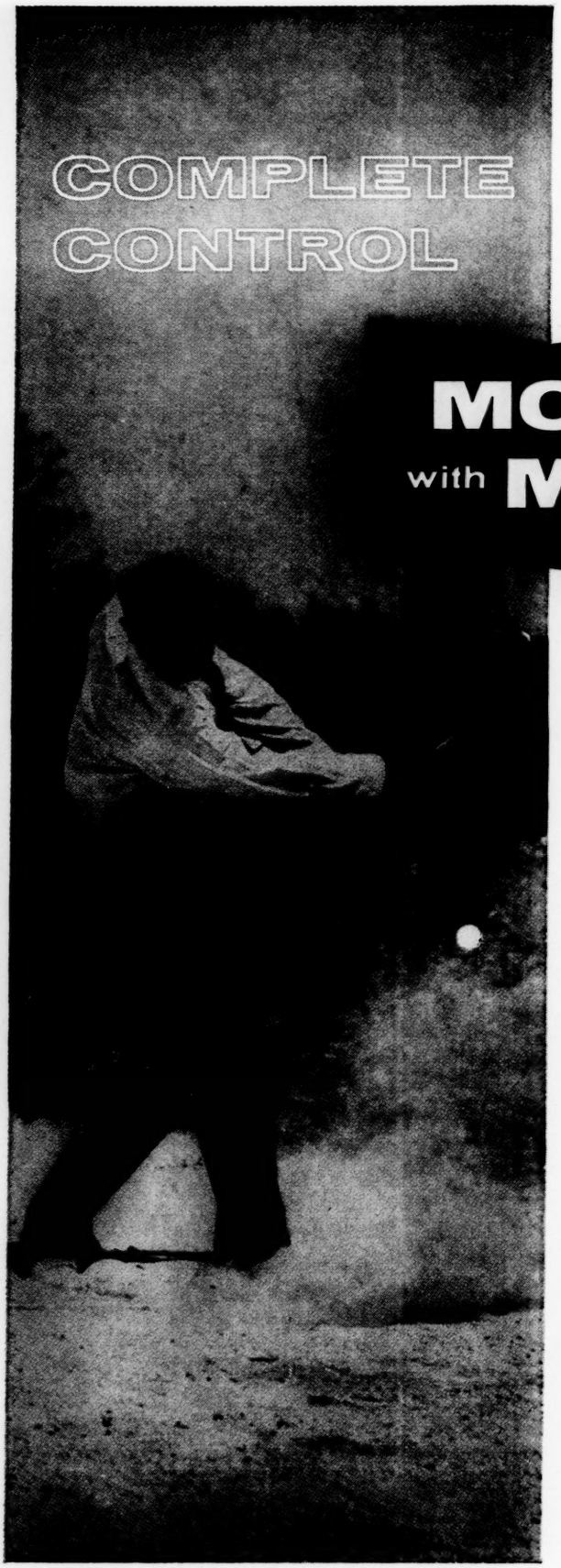
Tedral provides:

Theophylline	2 gr.
Ephedrine HCl	3/8 gr.
Phenobarbital	1/8 gr.

in boxes of 24, 120 and 1000 tablets

Tedral®

WARNER-CHILCOTT



MONODRAL with MEBARAL

for peptic ulcer • gastro-intestinal tension and irritability

An exclusive combination designed to relieve pain, reduce tension and promote healing through effective inhibitory central and vagal-parasympathetic actions influencing all known etiologic factors in peptic ulcer.

anticholinergic • sedative

with unusually high antisecretory action • dependable antispasmodic effect • no drowsiness

Isolates the Ulcer

Each tablet contains:

MONODRAL* bromide	5 mg
MEBARAL**	32 mg.

Dosage: 1 or 2 tablets three or four times daily.
Available on prescription only. Bottles of 100 tablets.

Winthrop LABORATORIES
New York 18, N.Y. • Windsor, Ont.

*Controls hyperacidity and hypermotility
**Sedates without drowsiness
Monodral (brand of penthienate) and Mebaral (brand of mephobarbital), trademarks reg. U.S. Pat. Off.

CONTENTS

The American Journal of Medicine

Vol. XX JUNE, 1956 No. 6

Editorial

The Levels of Disorganization . . . . . DeWitt Stetten, Jr. 817

Clinical Studies

Studies on Myocardial Metabolism. VI. Myocardial Metabolism in Congestive Failure
J. M. Blain, H. Schafer, A. L. Siegel and R. J. Bing 820

In this important study Dr. Bing and his collaborators apply their ingenious coronary sinus catheterization technics to the problem of myocardial metabolism in low output heart failure. While the results obtained have been foreshadowed by others it is nevertheless surprising to realize that there is no significant difference in oxygen consumption or pattern of substrate utilization, and therefore no apparent basic difference in energy production between the normal and the failing heart. The distinction between these states would seem to lie in inefficient utilization of available energy for muscular contraction, that is, in the contractile proteins of failing heart muscle.

Mechanisms of QRS Complex Prolongation in Man. Left Ventricular Conduction Disturbances . . . . . Robert P. Grant and Harold T. Dodge 834

The conventional electrocardiographic criteria of left bundle branch block, long a matter of general dissatisfaction, are here subjected to close scrutiny by vector analysis of a large series of cases with tracings obtained when ventricular conduction was normal and again when QRS was prolonged. This, then, may be considered to be a controlled study. It is demonstrated that left bundle branch block could not have been the cause of QRS prolongation in no less than one-third of these cases. In many such instances, QRS prolongation could be related to peri-infarction block; criteria for this differentiation are given. Progressive left ventricular hypertrophy was probably responsible for other instances of QRS prolongation. Many additional points of interest are brought out to make this paper a most illuminating contribution to a confused and controversial subject of immediate interest to the clinician.

Loud Presystolic Sounds over the Jugular Veins Associated with High Venous Pressure
William Dock 853

Dr. Dock notes an interesting auscultatory phenomenon, hitherto overlooked, the occurrence of a loud presystolic gallop sound recorded in a restricted area over the jugular vein of patients with right atrial hypertension. The sound appears near the peak of the jugular *a* wave. It is attributed to the impact of a wave of blood moving violently centrifugally at the height of atrial systole when the pressure in the right heart is markedly increased.

Contents continued on page 5

NEW CONCEPT IN URINE-SUGAR TESTING

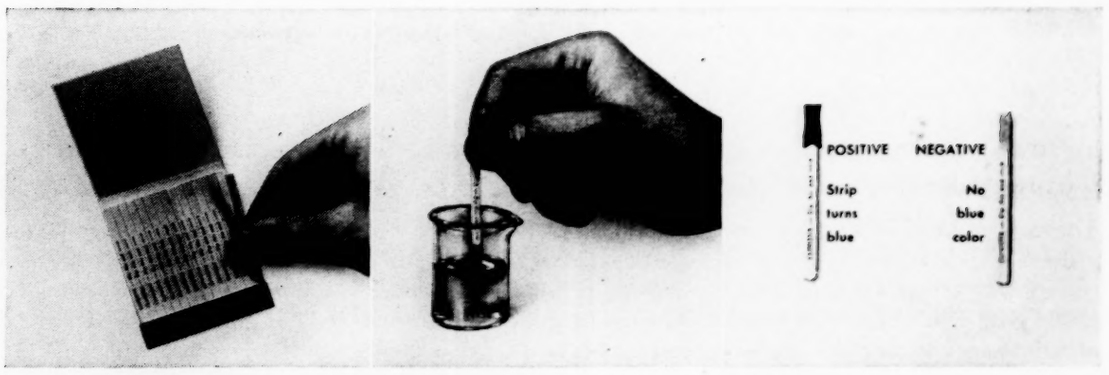
CLINISTIX

TRADEMARK

REAGENT STRIPS

specific enzyme test for urine glucose

just dip and read



complete specificity ... unaffected by non-glucose reducing substances ... differentiates glucose from other urine-sugars ... thousands of tests reveal no substance causing a false positive.

extreme sensitivity ... detects glucose concentrations of 0.1% or less.

utmost simplicity and convenience ... a CLINISTIX Reagent Strip moistened with urine turns blue when glucose is present.

qualitative accuracy ... used whenever presence or absence of glucose must be determined rapidly and frequently. CLINISTIX does not attempt to give quantitative results because so many factors in urine influence enzyme reactions.

economy ... CLINISTIX saves time and cuts costs ... each strip is a complete test rapidly performed without reagents and equipment.

available: Packets of 30 CLINISTIX Reagent Strips in cartons of 12—No. 2830.

AMES COMPANY, INC • ELKHART, INDIANA

Ames Company of Canada, Ltd., Toronto

13356

CONTENTS continued–June 1956

VOLUME TWENTY NUMBER SIX

Pendular Motion of the Mediastinum . . . PHILIP SAMET AND WILLIAM ANDERSON 860

While shifts in the mediastinum are readily recognized in chest roentgenograms and their diagnostic import appreciated, the full physiologic or pathophysiologic significance of the pendular motion of the mediastinum which they imply is usually overlooked. These implications are clearly brought out in the present careful study, which distinguishes five distinct types of mediastinal respiratory shift.

Congenital Heart Block
EPHRAIM DONOSO, EUGENE BRAUNWALD, SIDNEY JICK AND ARTHUR GRISHMAN 869

Complete heart block may justifiably be considered to be congenital in adults as well as in children when associated with anomalies of the heart, notably interventricular septal defect, and in the absence of other known causes. Eight such cases, so classified by the authors despite a paucity of information concerning the early cardiac findings in most instances, are described herein, and some unusual features are pointed out. Congenital heart block constitutes a significant fraction of the total incidence of complete heart block and may present quite different problems in management.

Relationship of Portal Hypertension to Ascites in Laennec's Cirrhosis
WILLIAM J. EISENMENGER AND WILLIAM F. NICKEL 879

Ever since hypertension in the portal venous system was first recognized it has been assumed to be an important factor in ascites formation, analogous to the role of hypertension in peripheral capillaries in the extravasation of fluid in peripheral edema. Recently, emphasis has been placed upon another factor in ascites formation, hypertension in the hepatic venous system. The relative importance of these two factors among many others, is still debatable, particularly in Laennec's cirrhosis. The present study strongly supports the significance of enhanced hydrostatic pressure in the extra- and intrahepatic portal bed in the persistent ascites formation in the patient with Laennec's cirrhosis by citing disappearance of ascites in five such patients very shortly after establishment of a portacaval shunt; peripheral edema, in contrast, was apt to become more marked. Among other things, these results suggest that intractable ascites in Laennec's cirrhosis may be an indication for shunt operations in selected cases, and not a contraindication.

Studies in Ammonia Metabolism. I. Ammonia Metabolism AND Glutamate Therapy in Hepatic Coma . . . . . B. EISEMAN, W. BAKEWELL AND G. CLARK 890

Blood ammonia determinations in the course of forty-four episodes of hepatic coma in thirty-one patients with cirrhosis confirmed the general association with elevated blood ammonia levels and led the authors to concur in the view that hepatic coma often is attributable to ammonia intoxication or to a related metabolic error. In such instances glutamate therapy was beneficial. In some cases of progressive hepatic failure, however, there was a dissociation in the two phenomena, indicating a more complex cause of hepatic coma.

Contents continued on page 7

ACTH
q 2 days
rather than q 12 h

One injection is effective for 24 to 72 hours or more

By adsorption of ACTH on zinc hydroxide, Cortrophin-Zinc permits extension of ACTH activity for a period of 1 to 3 days. This minimizes the therapeutic "ups and downs" which may occur during ACTH-in-gel therapy and provides smooth corticotropin action for a truly extended period.

Cortrophin-Zinc is easier to handle than gelatin preparations. An aqueous suspension, it flows easily through a 26-gauge needle, eliminating preheating, clogging syringes, and heavy-gauge needles that add to the pain.

Cortrophin-Zinc is supplied in 5 cc vials each cc containing 40 U.S.P. units of corticotropin with 2 mg. of zinc.

CORTROPHIN* ZINC†

a development of **Organon Inc.**
ORANGE, N. J.

*T.M.—Cortrophin Available in other countries as Cortrophine-Z †Patent Pending

CONTENTS continued–June 1956

VOLUME TWENTY NUMBER SIX

Reviews

Subacute Combined Degeneration of the Spinal Cord. Current Concepts of the Disease Process. Value of Serum Vitamin B_{12} Determinations in Clarifying Some of the Common Clinical Problems

MAURICE VICTOR AND ARNOLD A. LEAR 896

The authors begin with a concise but informative review of present knowledge of subacute combined degeneration of the spinal cord and its relationship to pernicious anemia. They stress the important point that the neurologic component of the disorder may introduce and, for years, dominate the clinical picture and that during this period the hematologic component, hence the diagnosis, may escape notice unless searchingly sought. This is particularly apt to occur if the patients receive folic acid, often as a minor constituent of some multivitamin preparation. Illustrative case reports effectively support the argument.

Treatment of Barbiturate Poisoning with or without Analeptics

JAMES E. ECKENHOFF AND WILLY DAM 912

As the authors remark, "for some reason, many physicians confronted with patients suffering from suspected barbiturate poisoning immediately think of analeptics" and it has taken some time to demonstrate the fallacy and danger of such thinking particularly if it leads to neglect of proper supportive therapy. This is clearly brought out in the text, largely based on an analysis of the large experience with barbiturate poisoning at the Narcotic Center in Copenhagen, Denmark. A rational and time-proved scheme of management of barbiturate poisoning in man is clearly and concisely described, and the restricted place of analeptics (in severe cases) indicated.

Seminar on Allergy

Life Stress and Allergy . . . . . STEWART WOLF 919

Dr. Wolf appropriately closes the Seminar on Allergy with an engaging and enlightening discussion of the relationship between personality adjustment and such clinical phenomena as "rhinitis" and bronchial asthma which fall in the category of allergic disorders. Citing specific cases, he puts the role of psychologic factors in perspective: In highly reactive subjects "any appropriate stimulus, be it irritant, allergen or emotional challenge, might produce a disturbance great enough to be recognizable and symptomatic."

Clinico-pathologic Conference

Hypertension, Proteinuria and Edema 929

Clinico-pathologic Conference (Washington University School of Medicine).

Research Society Abstracts

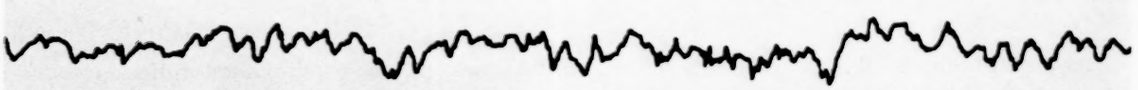
Southern Society for Clinical Research—Abstracts of Papers Presented at the Tenth Annual Meeting, New Orleans, Louisiana, January 21, 1956 941

Contents continued on page 9

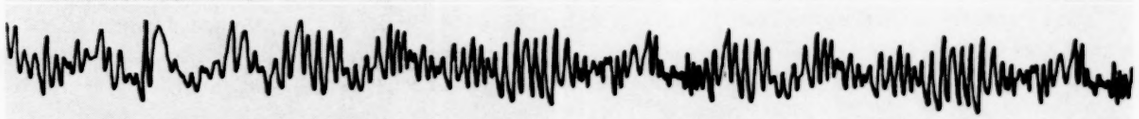
WHAT IS THE DIFFERENCE BETWEEN A TRANQUILIZER AND A SEDATIVE?

Comparison of the effect of Raudixin (tranquilizer) and a barbiturate (sedative) on the cortical electroencephalogram

No drug.



After Raudixin. E. E. G. not altered.



After barbiturate. Typical "spindling" effect.

Because barbiturates and other sedatives depress the cerebral cortex, the sedation achieved is accompanied by a reduction in mental alertness.

Raudixin acts in the area of the midbrain and diencephalon, and does not depress the cerebral cortex. Consequently, the tranquilizing (ataractic) effect achieved is generally free of loss of alertness.

RAUDIXIN

Squibb Whole Root Rauwolfia Serpentina

DOSAGE: 100 mg. b.i.d. initially; may be adjusted within a range of 50 mg. to 500 mg. daily. Most patients can be adequately maintained on 100 mg. to 200 mg. per day.

SUPPLY: 50 mg. and 100 mg. tablets; bottles of 100, 1000 and 5000.

SQUIBB *Squibb Quality—the Priceless Ingredient*

'RAUDIXIN'® IS A SQUIBB TRADEMARK

CONTENTS continued–June 1956

VOLUME TWENTY NUMBER SIX

Case Reports

Immunologic Agranulocytosis Due to Mercurial Diuretics
B. J. KOSZEWSKI AND T. F. HUBBARD 958

The phenomenon described in this well studied case must be distinctly uncommon but it is nevertheless of great interest from several points of view.

Combined Bacillary and Amebic Ulcerative Colitis Associated with Atypical Pneumonitis and Shigella-Positive Sputum . . . . EDWARD C. RAFFENSPERGER 964

An interesting case presenting pneumonitis and coliform organisms in the sputum before symptoms of the colon appeared.

Effect of Intramuscular Heparin on Antidodies in Idiopathic Acquired Hemolytic Anemia . . . . . KARL L. ROTH AND ABRAHAM M. FRUMIN 968

Intramuscular injection of heparin in a patient with idiopathic acquired hemolytic anemia caused transient decrease in free and bound antibodies, presumably due to rapid interaction with the heparin administered. This finding may have application in the management of acute crises.

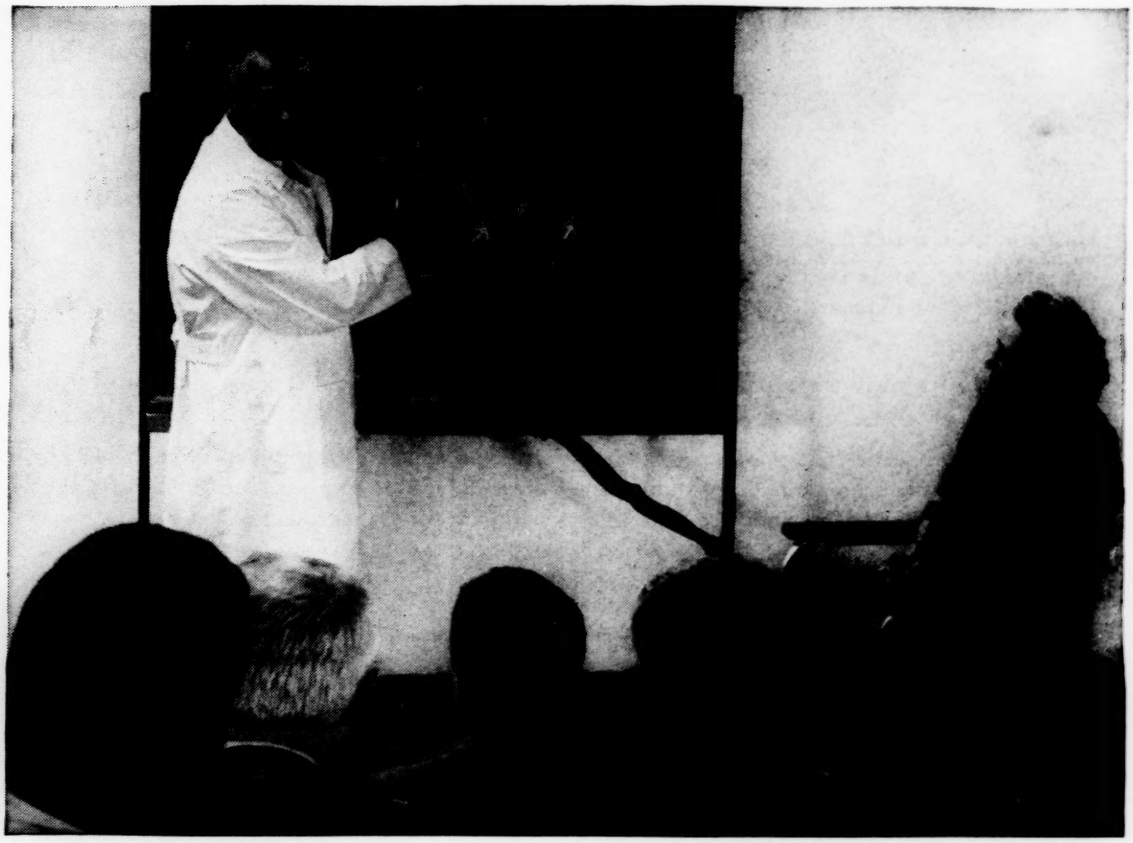
Author Index to Volume xx 971

Subject Index to Volume xx 973

Advertising Index on 3rd Cover

Change of address must reach us one month preceding month of issue.

adjusts anticoagulant-depressed prothrombin time



MAJOR ADVANTAGES: Action detectable within 15 minutes, prothrombin time normalized within 4 to 12 hours, bleeding checked in 3 to 6 hours.

EMULSION OF Mephyton®

(VITAMIN K_1 INJECTION, MERCK)

"It is shown that oil-soluble vitamin K_1 is more effective than any other agent now available in combating drug-induced hypoprothrombinemia."[1] However, the usefulness of Mephyton lies not only in overcoming bleeding emergencies, but also in adjusting upwards to safe therapeutic levels unduly prolonged prothrombin times. Mephyton permits the clinician to do this easily and without gross changes in the regular anticoagulant dosage. . . . "no untoward effects have been observed to follow the administration of vitamin K_1."[1]

INDICATIONS: Hypoprothrombinemia due to Dicumarol®, Cumopyran®, Tromexan®, Hedulin®, 'Dipaxin', and other prothrombin depressing agents; also when due to antibiotics, salicylates, obstructive jaundice, hepatic disease, and impaired gastrointestinal absorption.

SUPPLIED: In boxes of six 1-cc. ampuls, 50 mg. of vitamin K_1 per cc.

1. Gamble, J. R., *et al.*, *Arch. Int. Med.* 95:52, January 1955.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

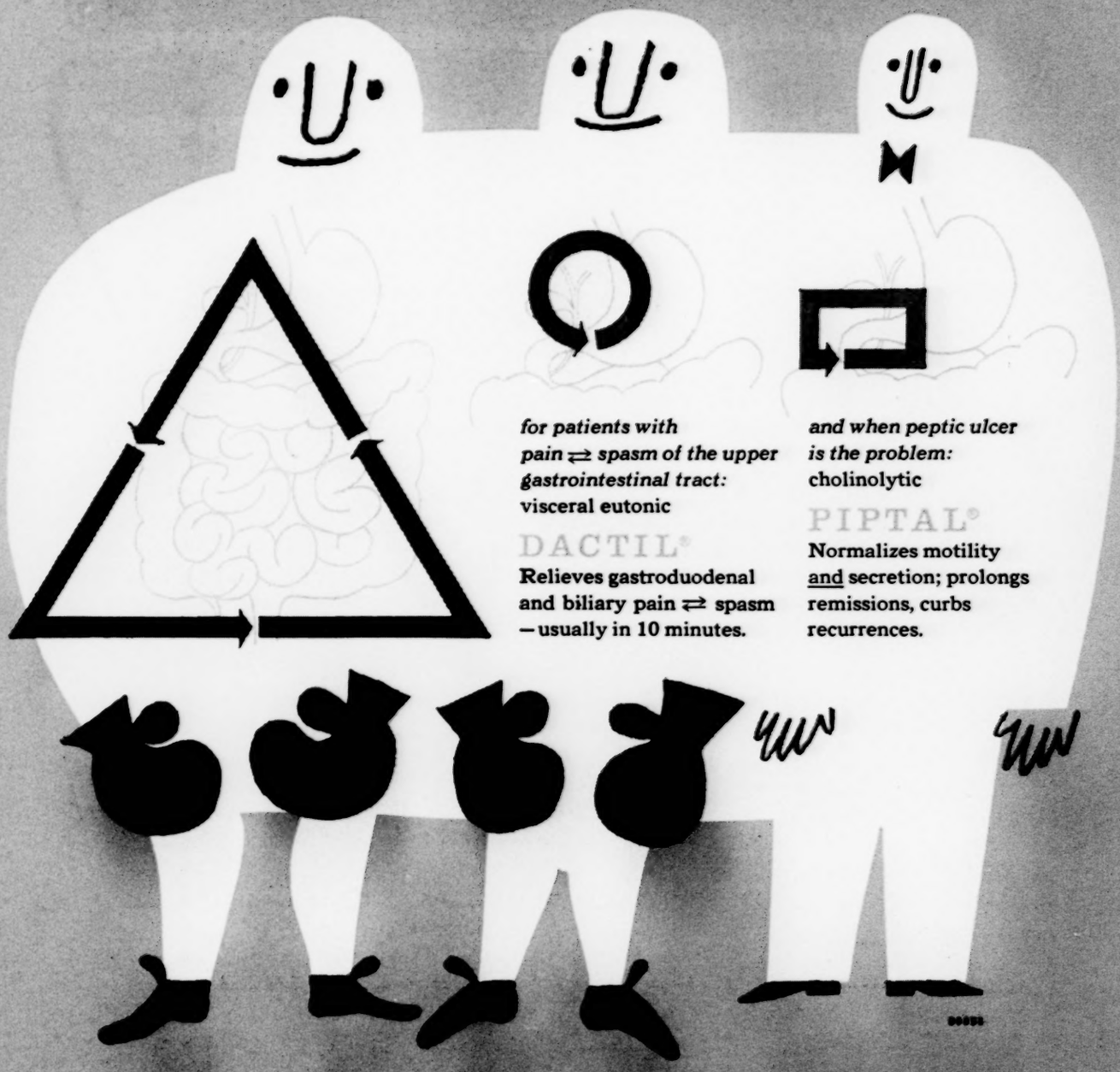
three patients...three piperidols

favorite for generalized G.I. dysfunction

TRIDAL

paired piperidol action

gives rapid, prolonged relief throughout the G.I. tract



for patients with pain ⇄ spasm of the upper gastrointestinal tract:
visceral eutonic

DACTIL®

Relieves gastroduodenal and biliary pain ⇄ spasm —usually in 10 minutes.

and when peptic ulcer is the problem:
cholinolytic

PIPTAL®

Normalizes motility and secretion; prolongs remissions, curbs recurrences.

Patients on TRIDAL, DACTIL or PIPTAL remain singularly free of anticholinergic-antispasmodic side effects.

LAKESIDE

a new substance

in a variety of rheumatic disorders...

"an 85% over-all effectiveness"[1]

the first orally effective lissive

for true spasmolysis
of skeletal muscle

McNEIL

your allergy patients need a lift

Plimasin®

(tripelennamine hydrochloride and methyl-phenidylacetate hydrochloride CIBA)

What with sneezing, wheezing and scratching, being allergic is fatiguing business. As a result your hypersensitive patients suffer from emotional depression in addition to their allergic symptoms.

Now, with Plimasin, you can give these patients a lift—and obviate sedative side effects. Plimasin is a combination of a proved antihistamine and Ritalin—a new, mild psychomotor stimulant. Plimasin not only relieves the symptoms of allergy but counteracts depression as well.

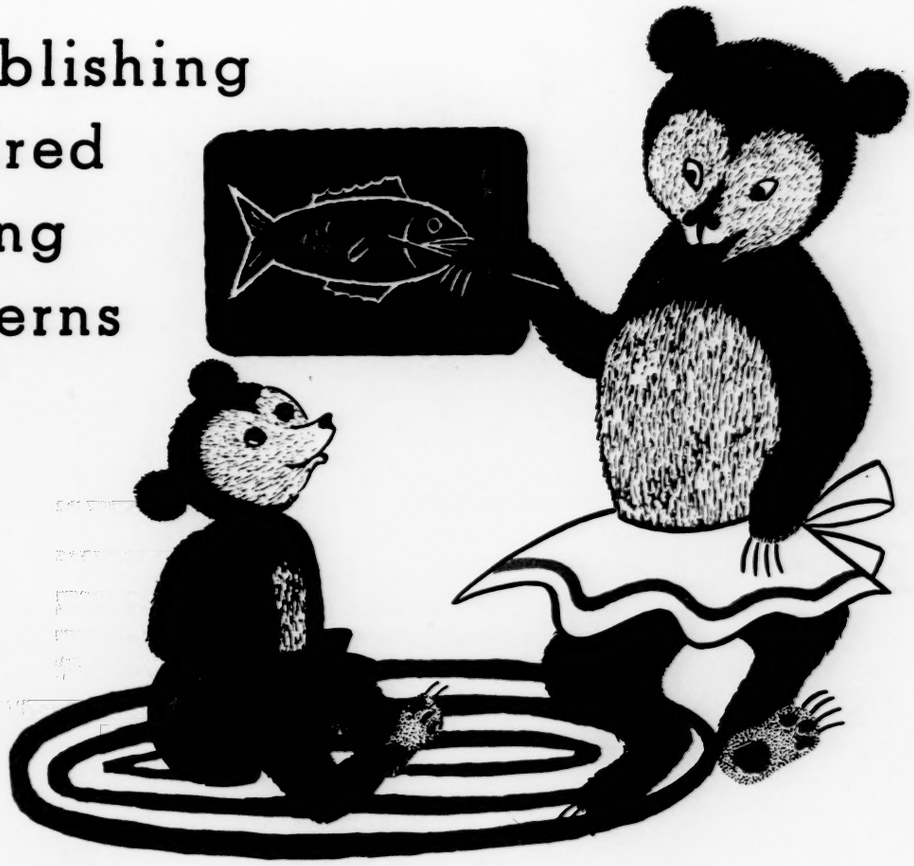
Dosage: 1 or 2 tablets every 4 to 6 hours if necessary.

Tablets (light blue, coated), each containing 25 mg. Pyribenzamine® hydrochloride (tripelennamine hydrochloride CIBA) and 5 mg. Ritalin® hydrochloride (methyl-phenidylacetate hydrochloride CIBA)

CIBA
SUMMIT, N.J.

R/3267M

establishing desired eating patterns



Obedrin®

and the 60-10-70 Basic Plan

In the development of good eating habits, medication is important, not only in initiating control, but also in maintaining normal weight.[1,2,3]

Obedrin contains:

- Methamphetamine for its anorexigenic and mood-lifting effects.
- Pentobarbital as a balancing agent, to guard against excitation.
- Vitamins B_1 and B_2 plus niacin to supplement the diet.
- Ascorbic acid to aid in the mobilization of tissue fluids.

Since Obedrin contains no artificial bulk, the hazards of impaction are avoided. The 60-10-70 Basic Plan provides for a balanced food intake, with sufficient protein and roughage.

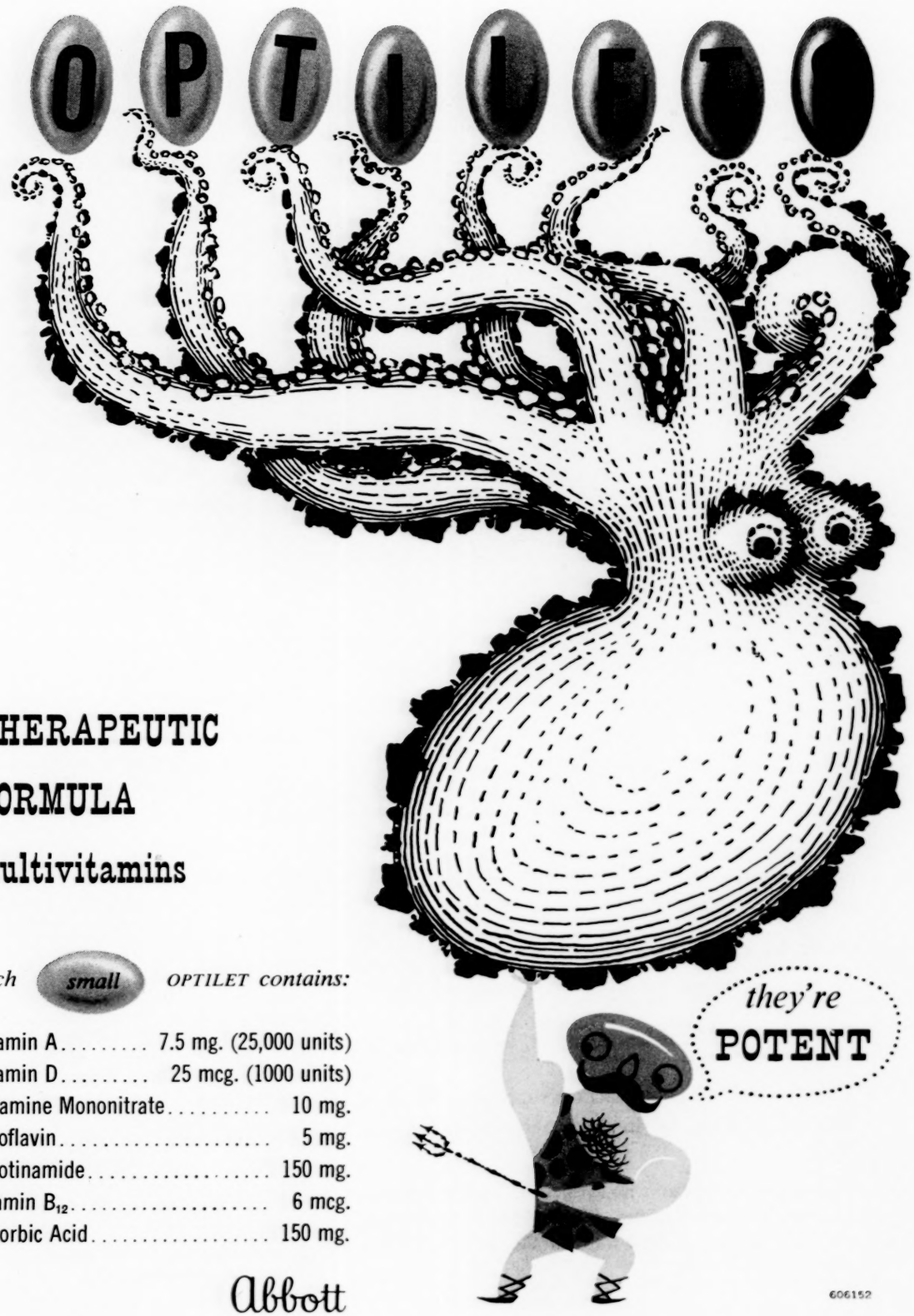
Formula

Semoxydrine HCl (Methamphetamine HCl) 5 mg.; Pentobarbital 20 mg.; Ascorbic acid 100 mg.; Thiamine HCl 0.5 mg.; Riboflavin 1 mg.; Niacin 5 mg.

1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).
2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

Write for 60-10-70 Menu pads, weight charts, and samples of Obedrin.

THE S. E. MASSENGILL COMPANY
BRISTOL, TENNESSEE



THERAPEUTIC FORMULA multivitamins

each small *OPTILET contains:*

Vitamin A	7.5 mg. (25,000 units)
Vitamin D	25 mcg. (1000 units)
Thiamine Mononitrate	10 mg.
Riboflavin	5 mg.
Nicotinamide	150 mg.
Vitamin B_{12}	6 mcg.
Ascorbic Acid	150 mg.

Abbott

606152

BON VOYAGE BEGINS WITH BONAMINE*

BRAND OF MECLIZINE HYDROCHLORIDE

longest-acting motion-sickness remedy[1] effective in low dosage . . . controls motion sensitivity symptoms in minutes . . . one dose usually prevents motion sickness for 24 hours.

In recommended dosage Bonamine is notably free from side reactions . . . supplied as: BONAMINE TABLETS, scored, tasteless, 25 mg. . . . BONAMINE CHEWING TABLETS, pleasantly mint flavored, 25 mg.

*Trademark 1. Report of Study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. 160:755 (March 3) 1956.

Pfizer PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.

for profound vasodilation in acute vasospastic disorders

ILIDAR

increases peripheral circulation and reduces vasospasm by (1) adrenergic blockade, and (2) direct vasodilation.

Provides relief from aching, numbness, tingling, and blanching of the extremities.

Exceptionally well tolerated.

ILIDAR® BRAND OF AZAPETINE

HOFFMANN-LA ROCHE INC • NUTLEY • N. J.

for prolonged vasodilation in chronic circulatory disorders

RONIACOL 'ROCHE'

RONIACOL® BRAND OF BETA-PYRIDYL CARBINOL

for control of fluid balance

By inhibiting carbonic anhydrase, DIAMOX produces prompt, ample diuresis. Taken in the morning, its effect ceases within 6-12 hours thereby permitting uninterrupted sleep at night.

This nontoxic drug—the most widely prescribed of its kind—is particularly suited to long-term use since patients do not readily develop tolerance.

DIAMOX is also effective in the treatment of glaucoma, epilepsy, premenstrual tension, the edema associated with toxemia of pregnancy, and edema caused by certain types of electrolytic imbalance.

250 mg. tablets for oral use
500 mg. ampuls for intravenous use in critical cases

Diamox*

Acetazolamide Lederle

the nonmercurial diuretic

LEDERLE LABORATORIES DIVISION *AMERICAN CYANAMID COMPANY* PEARL RIVER, NEW YORK

*REG. U. S. PAT. OFF.

Lederle

New ganglionic blocker lowers blood pressure consistently, predictably, usually with just 2 oral doses per day

Patients with moderate to severe essential hypertension, and even with malignant hypertension, often respond satisfactorily to a ganglionic blocking agent such as Ecolid. It can be used alone or — for maximal control of blood pressure with minimal side effects — in combination with other antihypertensive agents such as Serpasil or Apresoline.

Advantages

Ecolid has the following advantages over other ganglionic blockers:

- long action, usually requires only two oral doses per day
- rapid absorption — promptly reduces systolic and diastolic pressures
- consistent and predictable response — smoother control
- lower dosage required than with other ganglionic blockers
- minimal likelihood of drug tolerance

Clinical observations

In a study of four ganglionic blocking agents, Winsor[1] found that the "most effective agent was SU3088 [Ecolid]...." In another comparative study, Grimson[2] reported: "Results with Ecolid have been definitely more encouraging than those with pentolinium." Patients maintained on Ecolid state that they prefer this ganglionic blocking agent because of greater energy, improved appetite, less difficulty with constipation and fewer tablets to take.[2,3]

For complete information about Ecolid, particularly more details on dosage recommendations, management of undesired effects and precautions, contact your CIBA representative or write to Medical Service Division for booklet entitled "Ecolid — A New Ganglionic Blocker for Hypertension."

References:

1. Winsor, T.: Am. J. M. Sc. *230*:133 (Aug.) 1955. 2. Grimson, K. S.: J.A.M.A. *158*:359 (June 4) 1955. 3. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation *11*:733 (May) 1955. 4. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Angiology *6*:507 (Dec.) 1955. 5. Strawn, J. R., and Moyer, J. H.: Personal communication, 1955. 6. Maxwell, R. D. H., and Howie, T. J. G.: Brit. M. J. *2*:1189 (Nov. 12) 1955.

SUPPLIED: ECOLID Tablets (Rotocotes), 25 mg. (ivory) and 50 mg. (pink).

DOSAGE: Dosage must be adjusted to the individual patient. Below is a typical plan by which treatment may be initiated.

Ambulatory patients		
DAY	A.M.	P.M.
1	25 mg.	—
2	25 mg.	25 mg.
3	50 mg.	25 mg.
4	50 mg.	50 mg.
5	75 mg.	50 mg.
6	75 mg.	75 mg.
7	100 mg.	75 mg.
8	100 mg.	100 mg.

Hospitalized patients		
DAY	A.M.	P.M.
1	50 mg.	—
2	50 mg.	50 mg.
3	100 mg.	50 mg.
4	100 mg.	100 mg.

to optimal response

Ecolid T.M.

chloride

(chlorisondamine chloride CIBA)

SERPASIL® (reserpine CIBA)
APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA)
ROTOCOTES T.M. (dry-compressed, coated tablets CIBA)

REPRESENTATIVE CLINICAL STUDIES OF **Ecolid***

Number of Patients	Initial Oral Dosage	Responses	Duration of Action	References
		[illegible] ganglionic [illegible] of Ecolid were [illegible] and greater hypotensive effect was obtained. Rapid absorption and long duration of hypotensive action.	Postural hypotension lasted 13.4 hours in 5 "test" patients receiving doses of 150 mg.	1
		Blood pressure in 20 well controlled; reductions lasted twice as long as those induced by pentolinium. Each of 10 patients with previous experience with hexamethonium preferred Ecolid. Less difficulty with constipation; appetite improved; greater energy.	**	2
		Hypertension in 18 well controlled. Supine blood pressure reduced without tachycardia. Constipation occurred infrequently.	Supine blood pressure lowered for 12 hours or more with single oral doses of 50 to 100 mg.	3,4
		25 responded well; 14 of these became normotensive. All patients received reserpine as base therapy.	**	5
		Blood pressure of all 12 satisfactorily controlled. Systolic blood pressure lowered average of 76 mm. Diastolic blood pressure lowered average of 42 mm.	**	6

*[illegible] a total of 54 investigators have reported on the use of Ecolid in more than 500 patients. They were practically unanimous in the opinion that it [illegible] was highly effective. Nearly all commented on the prolonged duration of action — about 8 to 12 hours — which permits a convenient dosage schedule in most cases.

**Information not available

SUMMIT N. J.

HOW OLD IS OLD?

"The really old people are those 10 years older than myself."[1]

"In the lay mind, anyone past 60 is ready for the discard . . ."[2]

". . . there are only three principal phases in the span of life: infancy, adolescence and senescence."[3]

"One finds alert, interesting, active folks in the 80's and, on the other hand, there are people in the 20's and 30's who have all the characteristics of old age."[4]

THE REAL QUESTION

To the physician on the firing line of daily practice, the question of "how old is old?" seems academic. To him, a more valid question is "How can I allay the effects of the aging process?"

FIVE PROBLEMS IN AGING

The answer, according to most authorities, is manifold, for five treatable problems seem to predominate. One, obviously, is gonadal hormone decline. Another is mild anemia. A third is the decreased production of gastric and digestive enzymes. Mineral-vitamin deficiency is the fourth. And the fifth — perhaps most important — is inadequate high-quality protein intake.

THERAPY FOR AGING

Judging from this confused clinical picture of aging, therapy for the problem would appear difficult. However, most physicians agree that a product which could correct most or all of these five commonest problems would remove past obstacles to satisfactory response. Such a product would, essentially, be true "preventive geriatrics."

NEOBON'S COMPREHENSIVE FORMULA

NEOBON®, a product of Roerig research, is a blended combination of the five most commonly indicated factors for prevention or treatment of the nonacute conditions of aging. Each soft, soluble capsule provides:

Non-stimulatory gonadal hormone replacement

balanced hematinic component

digestant enzyme replacement

specially formulated mineral-vitamin combination

new lysine, for protein improvement*

* Protein deficiency among the aging apparently stems from their excessive intake of white-flour foods which furnish incomplete protein of low biologic value. White bread protein, for example, has been shown by nutrition studies in animals[5] to be deficient only in the amino acid, lysine. In human subjects metabolic determinations indicate that the addition of supplemental lysine to a basal white-flour protein diet can convert a negative nitrogen balance into a positive one.[6]

A WORD ABOUT SYMPTOMATOLOGY

In spite of jokes to the contrary, the patient who states in the professional office that "old age is creeping up" is a rare bird indeed.

Seldom is old age the presenting complaint. Thus the physician, after correcting the specific complaints, must re-evaluate the whole person to judge his candidacy for "preventive geriatrics." Such people have much to gain from NEOBON therapy. The rewards are fuller, more active, more pleasurable years for patients past 40. The daily dose (3 capsules) of NEOBON provides:

L-lysine	150 mg.
Methyltestosterone	3 mg.
Ethinyl Estradiol	0.018 mg.
Pancreatic Substance***	150 mg.
Glutamic Acid	90 mg.
Rutin	15 mg.
Vitamin A (Palmitate)	6,000 U.S.P. Units
Vitamin D (Irradiated Ergosterol)	600 U.S.P. Units
Vitamin E (as Tocopheryl Acetate)	15 I.U.
Calcium Pantothenate	15 mg.
Thiamine Mononitrate (Vitamin B_1)	1.5 mg.
Riboflavin (Vitamin B_2)	1.5 mg.
Pyridoxine Hydrochloride (Vitamin B_6)	1.5 mg.
Niacinamide	150 mg.
Ascorbic Acid (Vitamin C)	150 mg.
Vitamin B_{12} (Oral Concentrate)	3 mcg.
Folic Acid	0.3 mg.
Liver-Stomach Substance**	300 mg.
Iron (from Ferrous Gluconate)	10.2 mg.
Cobalt (from Cobaltous Sulfate)	0.1 mg.
Molybdenum (from Sodium Molybdate)	2 mg.
Copper (from Cupric Sulfate)	1 mg.
Manganese (from Manganous Sulfate)	1 mg.
Magnesium (from Magnesium Sulfate)	6 mg.
Iodine (from Potassium Iodide)	0.15 mg.
Potassium (from Potassium Sulfate)	5 mg.
Zinc (from Zinc Sulfate)	1.2 mg.

**Enzymatically active defatted material obtained from 1,500 mg. whole fresh liver and stomach.

***Enzymatically active defatted material obtained from 750 mg. of whole fresh pancreas.

Dosage: 3 capsules daily, with meals.

Supplied: Bottles of 60 capsules, prescription only.

NEW NEOBON® LIQUID

A GERIATRIC TONIC

Now also available for your consideration is NEOBON LIQUID, which provides hematinic action, improved carbohydrate and protein utilization, gonadal and thyroid hormone supplementation and a mild antidepressant action.

The pleasant tasting liquid is especially indicated when a combined attack against nutritional, physiological and mental depression is indicated. Each teaspoonful (5 cc.) of pleasant-tasting NEOBON LIQUID contains:

Ferrous Gluconate	30 mg.
Ascorbic Acid	50 mg.
d-Amphetamine Sulfate	0.5 mg.
Folic Acid	167 mcg.
Vitamin B_{12}	2.5 mcg.
l-Thyroxine	0.1 mg.
Ethinyl Estradiol	1 mcg.
Methyltestosterone	1 mg.
Liver Fraction I	25 mg.
Ethyl Alcohol	0.5 cc.

Dosage: One teaspoonful twice daily before meals, or as required.

Supplied: In 16 fluid ounce bottles, prescription only.

Bibliography

1. Anonymous. 2. Rosenthal, P.: Geriatrics 10:382 (August) 1955. 3. Lansing, A. I.: Symposium on Problems of Gerontology, National Symposium Series No. 9 (August) 1954. 4. Mason-Hohl, E.: Quoted in W. Va. Med. J. 51:16 (January) 1955. 5. Rosenberg, H. R., et al.: Arch. Biochem. and Biophys. 49:263, 1954. 6. Bricker, M., Mitchell, H. H. and Kinsman, G. M.: J. Nutrition 30:269, 1945. 7. Masters, W. H. and Ballew, J. W.: Geriatrics 10:1, 1 (January) 1955.

ROERIG Rx *CHICAGO 11, ILLINOIS*

Erythrocin in the treatment of pharyngitis*

9/12/55

DISCHARGE SUMMARY

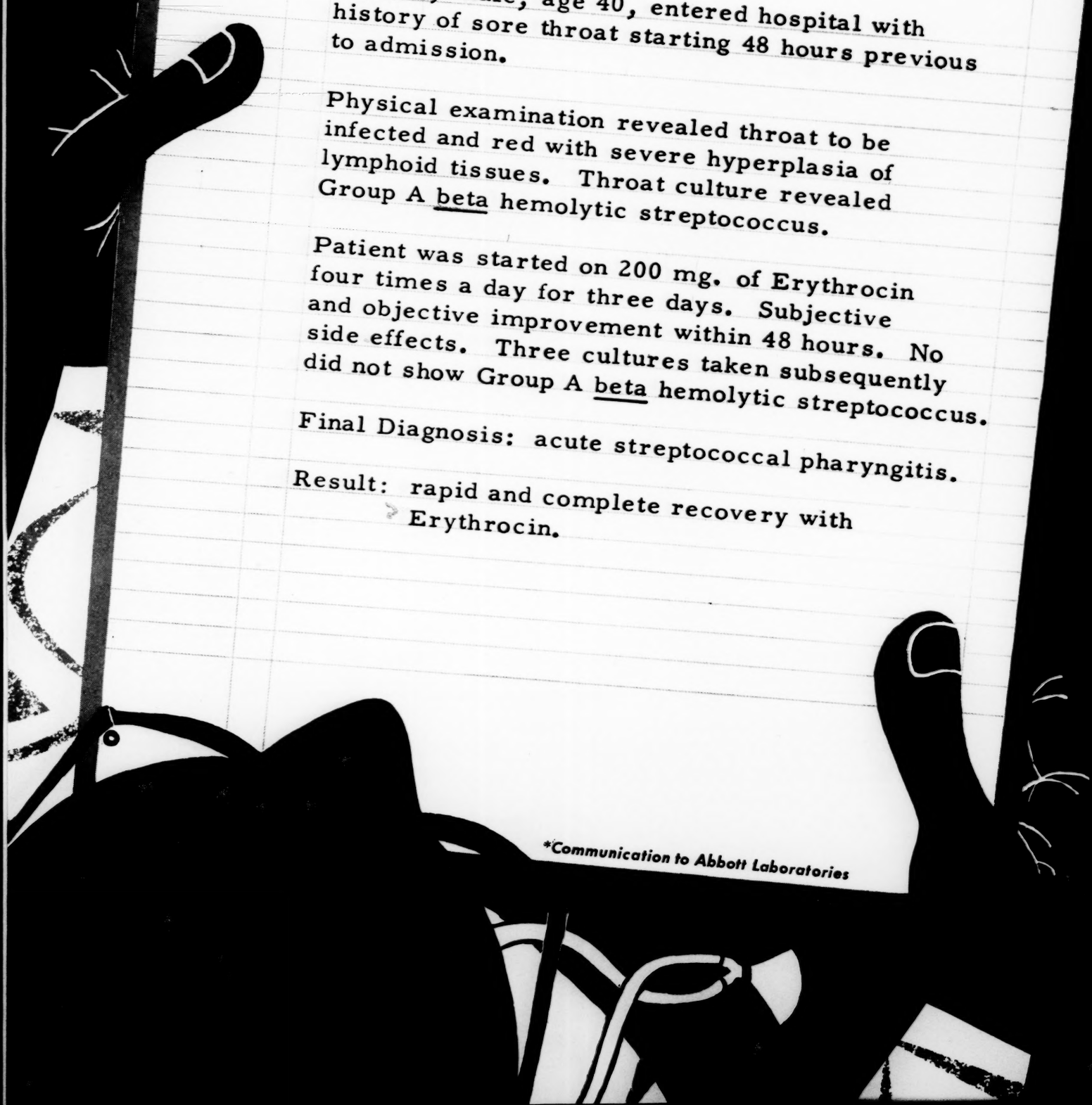
Patient, male, age 40, entered hospital with history of sore throat starting 48 hours previous to admission.

Physical examination revealed throat to be infected and red with severe hyperplasia of lymphoid tissues. Throat culture revealed Group A beta hemolytic streptococcus.

Patient was started on 200 mg. of Erythrocin four times a day for three days. Subjective and objective improvement within 48 hours. No side effects. Three cultures taken subsequently did not show Group A beta hemolytic streptococcus.

Final Diagnosis: acute streptococcal pharyngitis.

Result: rapid and complete recovery with Erythrocin.



*Communication to Abbott Laboratories

specific against coccic infections

Specific—because you can actually pinpoint the therapy for coccic infections. That's because you know most bacterial respiratory infections are caused by staph-, strep- and pneumococci. And these are the very organisms most sensitive to ERYTHROCIN—even when they resist penicillin and other antibiotics.

filmtab®

Erythrocin®

(Erythromycin Stearate, Abbott)

STEARATE

with little risk of side effects

Low toxicity—because ERYTHROCIN (in contrast to many other antibiotics) rarely alters intestinal flora. Thus, patients seldom get gastroenteral side effects. Or loss of vitamin synthesis in the intestine. No allergic reactions, either. *Filmtab* ERYTHROCIN Stearate (100 and 250 mg.), bottles of 25 and 100. Abbott

filmtab®

Erythrocin®

(Erythromycin Stearate, Abbott)

STEARATE

®Filmtab—film-sealed tablets; pat. applied for

605169

"... may be unique as a wide-spectrum antimicrobial agent that is bactericidal, relatively nontoxic, and does not invoke resistant mutants."[1]

Furadantin®

BRAND OF NITROFURANTOIN

in acute and chronic pyelonephritis, cystitis, prostatitis

Percentage of Effectiveness of Furadantin Against Various Strains of Bacteria in Vitro

	Aerobacter aerogenes	Proteus sp.	Paracolobactrum sp.	Micrococcus pyogenes	Streptococcus pyogenes	Escherichia coli	Pseudomonas aeruginosa
Furadantin	82.1	66.6	31.2	91.9	93.9	60.0	13.3
Antibiotic A	71.4	55.5	25.0	93.5	96.9	66.0	26.6
Dihydrostreptomycin	14.2	25.9	12.5	38.7	27.2	28.0	6.6
Antibiotic B	3.5	0	0	66.1	63.6	0	2.2
Penicillin	3.5	0	0	27.4	39.3	0	0
Antibiotic C	14.2	7.4	18.7	46.7	72.6	22.0	11.1

ADAPTED FROM PERRY[2]

Furadantin's "high degree of effectiveness against bacteria responsible for urinary tract infections is brought out by this study."[2]

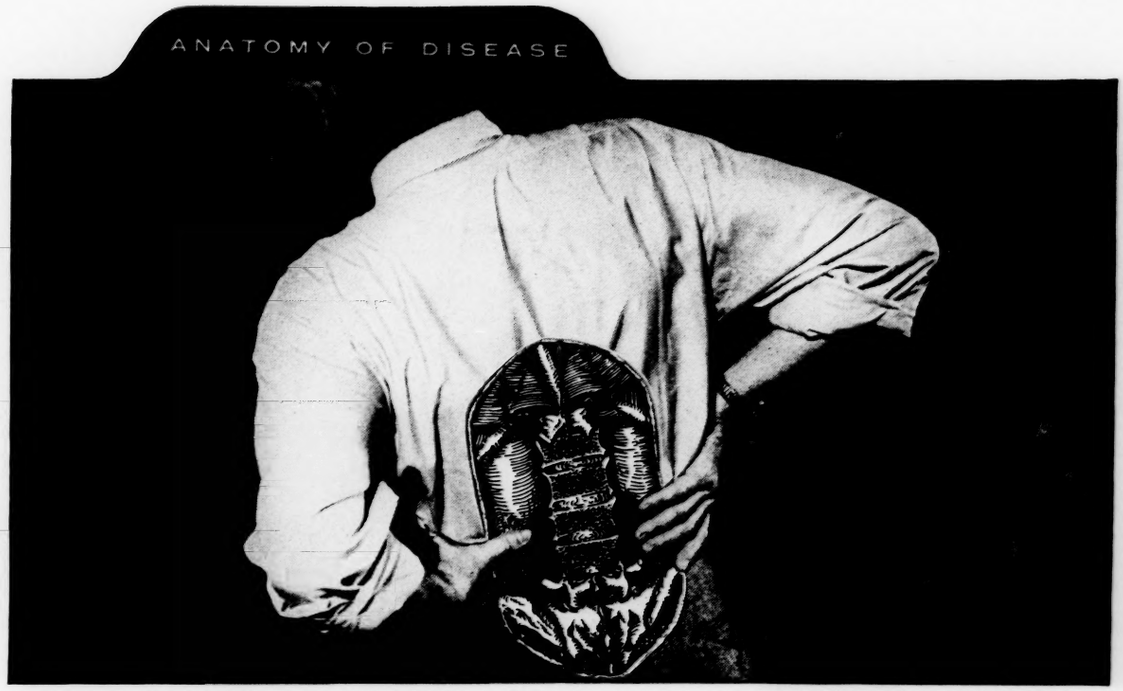
Furadantin dosage—simple and safe: Average adult dose is 100 mg., q.i.d., (at mealtime, and on retiring, with food or milk). Average daily dosage for children is 5 to 7 mg./Kg. in four divided doses.

SUPPLIED: Tablets, 50 and 100 mg., bottles of 25 and 100.
Oral Suspension, 5 mg. per cc., bottle of 118 cc.

REFERENCES: 1. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955. 2. Perry, R. E., Jr.: North Carolina M. J. 16:567, 1955.

NITROFURANS—A NEW CLASS OF ANTIMICROBIALS—NEITHER ANTIBIOTICS NOR SULFAS

Eaton LABORATORIES



1. Time-tested Armyl...
2. ...combined with *small* amounts of corticoid

for better results in rheumatic and arthritic conditions

Armyl+F

Synergistic action of the combination of agents in Armyl+F results in significantly better patient response with extremely low doses of corticoid.

Each Armyl + F capsulette contains:

Compound F (hydrocortisone-free alcohol)	2.0 mg.
Potassium Salicylate (5 gr.)	0.30 Gm.
Potassium Para-aminobenzoate (5 gr.)	0.30 Gm.
Ascorbic Acid U.S.P.	50 mg.

Bottles of 50 capsulettes.

if salicylates alone can control the patient

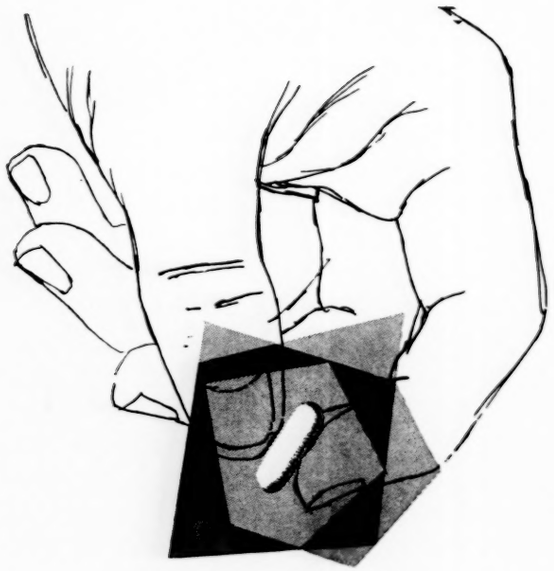
Armyl® produces high salicylate blood levels . . . relieves pain . . . provides antihemorrhagic protection.

Each enteric-coated tablet contains:

Sodium Salicylate	0.3 Gm.
Sodium Para-aminobenzoate (5 gr.)	0.3 Gm.
Ascorbic Acid U.S.P. (50 mg.)	0.05 Gm.

Bottles of 100. Also available: Armyl with ½ gr. Phenobarbital; Armyl Sodium-Free; Armyl Sodium-Free with ½ gr. Phenobarbital.

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS



just 1 tablet daily

helps meet the

increased nutritional

requirements of pregnancy

ENGRAN

SQUIBB VITAMIN-MINERAL SUPPLEMENT

new formula

new small size capsule-shaped tablet

Each Engran Tablet supplies:

Vitamin A (synthetic)	5,000 U.S.P. Units	Calcium, elemental (as calcium carbonate)	150 mg.
Vitamin D	500 U.S.P. Units	Iron, elemental (as ferrous sulfate exsiccated)	10 mg.
Thiamine mononitrate	3 mg.	Iodine (as potassium iodide)	0.15 mg.
Riboflavin	3 mg.	Potassium (as the sulfate)	5 mg.
Pyridoxine HCl	2 mg.	Cobalt (as the sulfate)	0.1 mg.
Vitamin B_{12} activity concentrate	2 mcgm.	Copper (as the sulfate)	1 mg.
Folic acid	0.25 mg.	Magnesium (as the oxide)	6 mg.
Niacinamide	20 mg.	Manganese (as the sulfate)	1 mg.
Calcium pantothenate	5 mg.	Zinc (as the sulfate)	1.5 mg.
Ascorbic acid	75 mg.		

Supplied in bottles of 100 and 1000 capsule-shaped tablets

SQUIBB

"ENGRAN"® IS A SQUIBB TRADEMARK

BETTER

results are obtained with STERANE[1]—3 to 5 times more active than hydrocortisone or cortisone.

BREATHING

capacity is greatly enhanced. "Relief of symptoms is more complete and maintained for longer periods with relatively small doses."[2]

BALANCE

of minerals and fluids usually remains undisturbed. This proves "especially advantageous in those patients with cardiac failure requiring therapy . . ."[3]

in bronchial asthma

Sterane®

brand of prednisolone

Supplied: White, 5 mg. oral tablets, bottles of 20 and 100. Pink, 1 mg. oral tablets, bottles of 100. Both deep-scored.

1. Johnston, T. G., and Cazort, A. G.: J. Allergy 27:90, 1956. 2. Schwartz, E.: New York J. Med. 56:570, 1956. 3. Schiller, I. W., et al.: J. Allergy 27:96, 1956.

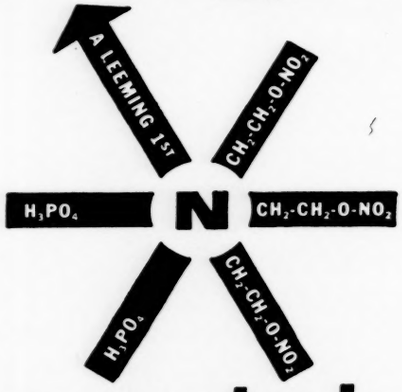
PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

Metamine®

triethanolamine trinitrate biphosphate, LEEMING, tablets 2 mg. Bottles of 50 and 500
Dose: 1 or 2 tablets after each meal and at bedtime.

smallest dose lowest toxicity unique amino nitrate

protects
8 out of 10
patients
against angina pectoris

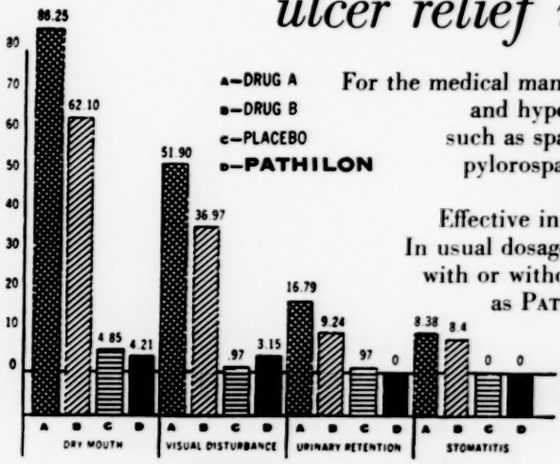


Thos. Leeming & Co., Inc., 155 East 44th Street, New York 17, N. Y.

HILON*

Iodide
Tridihexethyl iodide *Lederle*
Tablets 25 mg.

ulcer relief with few side effects[1]



For the medical management of peptic ulcer, gastric hyperacidity and hypermotility, gastrointestinal spastic conditions such as spastic and irritable colon, functional diarrhea, pylorospasm, and hypermotility of the small intestine that is not associated with organic change.[2]
Effective in relieving pain due to smooth muscle spasm. In usual dosage, undesirable side effects are rare. Available with or without added phenobarbital, 15 mg. Also offered as PATHILON Parenteral, 10 mg./cc.—1 cc. ampuls.

1. "Evaluation of Drugs in the Treatment of Peptic Ulcer" by J. M. Ruffin, M. D.; D. Cayer, M. D.; J. S. Atwater, M. D., and B. G. Oren, M. D., Exhibit at A.M.A. Meeting, Atlantic City, June, 1955.
2. J.A.M.A. 160:389 (Feb. 4) 1956.

LEDERLE LABORATORIES DIVISION AMERICAN CYANAMID COMPANY PEARL RIVER, NEW YORK
*REG. U.S. PAT. OFF.

REPRINT ORDER FORM

THE AMERICAN JOURNAL OF MEDICINE, 49 W. 45th St., New York 36, N. Y.

Please send me the following Seminars reprinted from the AMERICAN JOURNAL OF MEDICINE:

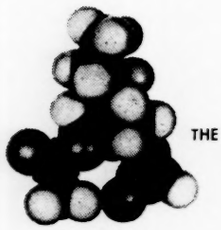
☐ GASTROINTESTINAL PHYSIOLOGY	$2.00
☐ BLOOD COAGULATION	$2.00
☐ ANTI HYPERTENSIVE DRUGS	$2.00
☐ HEMOLYTIC ANEMIAS	$2.00
☐ CARBOHYDRATE METABOLISM	$2.00

Enclosed is my check

NAME_____

ADDRESS_____

CITY_____ STATE_____



THE MILTOWN MOLECULE

A tranquilizer well suited for prolonged therapy

NO ORGANIC CONTRAINDICATIONS

reported to date

- well tolerated, non-addictive, essentially non-toxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness
- chemically unrelated to chlorpromazine or reserpine
- does not produce significant depression
- orally effective within 30 minutes for a period of 6 hours

Indications: anxiety and tension states, muscle spasm.

Miltown®

the original meprobamate— 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate—U.S. Patent 2,724,720

SUPPLIED: 400 mg. scored tablets. Usual dose: 1 or 2 tablets t.i.d.

DISCOVERED AND INTRODUCED by Wallace Laboratories, New Brunswick, N. J.

Literature and Samples Available on Request

antihistaminic benefits of Benadryl
neutralizing action of zirconium

ZIRADRYL® LOTION

Benadryl® Hydrochloride with Zirconium

an old favorite in a new form

ZIRADRYL Lotion provides the same recognized clinical advantages as **ZIRADRYL** Cream. Antihistaminic-antipruritic properties of Benadryl are combined with the urushiol-neutralizing action of zirconium for effective prevention or treatment of ivy or oak poisoning.

protects against rhus dermatitis

if applied before or soon after exposure.

relieves rhus dermatitis

and reduces spreading if applied after dermatitis appears.

ZIRADRYL Lotion is supplied in 6-ounce bottles.
ZIRADRYL Cream is supplied in 1-ounce tubes.

MEDICAMENTA VERA

PARKE, DAVIS & COMPANY DETROIT, MICHIGAN

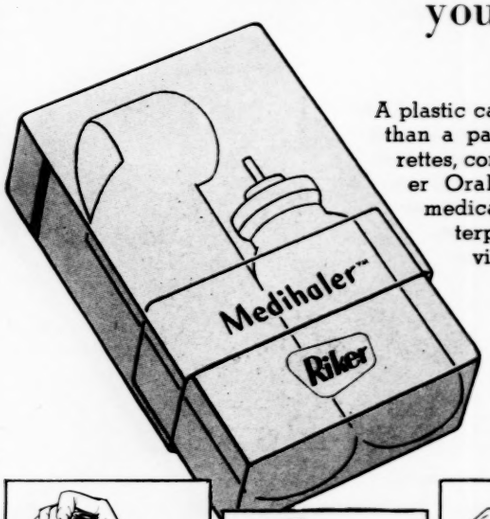
B0084

New... *and a Major Advance in Treatment of*

ASTHMA

MEDIHALER™

Fully effective nebulization with your favorite bronchodilator*



A plastic case; little larger than a package of cigarettes, contains Medihaler Oral Adapter and medication* (in shatterproof, spillproof vial).

Insert valve of medication vial snugly into Adapter.

Hold as shown, close lips around Adapter, and inhale while pressing vial down against Adapter.

Package is conveniently carried in pocket or purse. Inconspicuous, notably safe, dependable.

Simple to administer to children. Uniform dose, no spilling, no glass to break.

•

One or two applications abort most attacks. Rarely is more required.

UNIFORM DOSAGE

SELF POWERED

ECONOMICAL

a) Unbreakable Adapter
b) No Medication Loss from Spillage or Oxidation

UNIFORM PARTICLE SIZE

80% between ½ and 4 microns radius

•

***MEDIHALER-EPI™**

0.5% solution of epinephrine HCl U.S.P.

***MEDIHALER-ISO™**

0.25% solution of isoproterenol HCl U.S.P.

follow this simple form of Rx

Riker
LOS ANGELES

Rx Medihaler-Iso and Medihaler Oral Adapter

ANOTHER RIKER FIRST

Upjohn

Ulcer protection that lasts all night:

Pamine* BROMIDE

Tablets

Each tablet contains:
Methscopolamine bromide ..... 2.5 mg.

Average dosage (ulcer):
One tablet one-half hour before meals, and 1 to 2 tablets at bedtime.

Supplied: Bottles of 100 and 500 tablets

Syrup

Each 5 cc. (approx. 1 tsp.) contains:
Methscopolamine bromide ..... 1.25 mg.

Dosage:
1 to 2 teaspoonfuls three or four times daily.

Supplied: Bottles of 4 fluidounces

Sterile Solution

Each cc. contains:
Methscopolamine bromide ..... 1 mg.

Dosage:
0.25 to 1.0 mg. (¼ to 1 cc.), at intervals of 6 to 8 hours, subcutaneously or intramuscularly.

Supplied: Vials of 1 cc.

*TRADEMARK, REG. U. S. PAT. OFF.—THE UPJOHN BRAND OF METHSCOPOLAMINE

The Upjohn Company, Kalamazoo, Michigan

forecast:

picnics and pollen

time for

Tyzine®

brand of tetrahydrozoline hydrochloride

for relief of allergic nasal congestion in minutes for hours

When hay fever and other seasonal allergies have a field day, remember the "superior"[1-3] decongestive properties of TYZINE . . . effective immediately and lasting up to 6 hours or longer after a single application . . . odorless, tasteless . . . free of sting, burn, irritation and rebound congestion.

Supplied:

TYZINE Nasal Solution, 1-oz. dropper bottles, 0.1%. Nasal Spray, 15 cc., in plastic bottles, 0.1%. Pediatric Nasal Drops, 1/2-oz. bottles, 0.05%, with calibrated dropper for precise dosage.

Note: As with certain other widely used nasal decongestants, overdosage may cause drowsiness in infants and children. Although no effect on blood pressure has been reported, it is recommended that caution be observed in treating hypertensive or hyperthyroid patients.

1. Pace, W. G.: Mil. Med. 118:34, 1956.
2. Graves, J. W.: Eye, Ear, Nose & Throat Month. 34:670, 1955.
3. Menger, H. C.: New York J. Med. 55:812, 1955.

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

new

Azo Gantrisin

Especially for Urinary Tract Infections

Azo Gantrisin provides -- in a single tablet -- the wide antibacterial spectrum of Gantrisin plus the local pain-relieving action of a widely accepted urinary tract analgesic.

Advantages of Azo Gantrisin: Effective antibacterial concentrations in blood as well as urine; prompt relief of local discomfort; rapid appearance of orange-red dye in urine also has favorable psychologic effect.

Each tablet contains 0.5 Gm Gantrisin 'Roche' plus 50 mg phenylazo-diamino-pyridine HCl.

Hoffmann - La Roche Inc
~~Nutley • N.J.~~

ROCHE

Gantrisin® - brand of sulfisoxazole

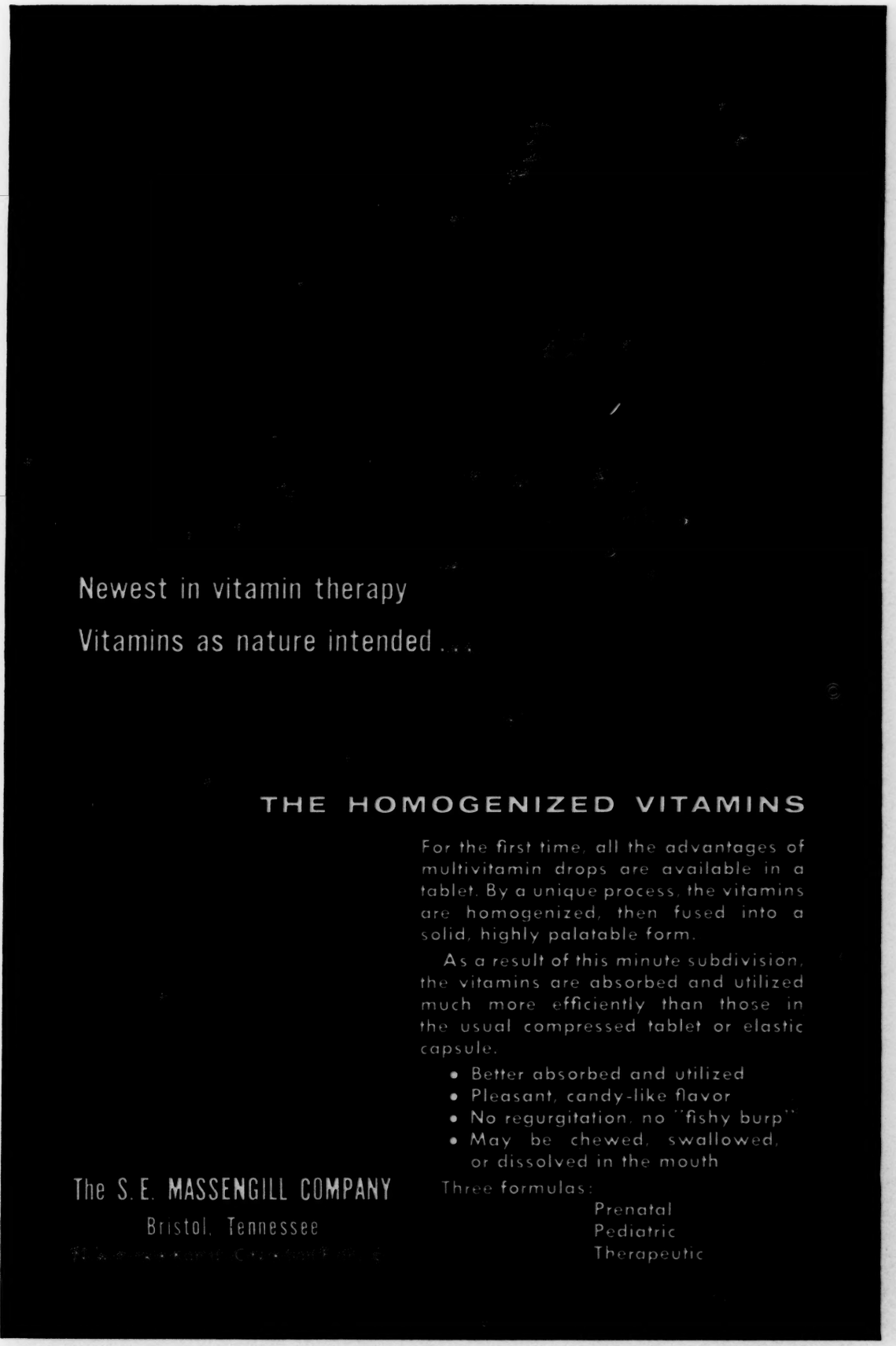
For patients who take their troubles to bed—

Noludar 'Roche' brings welcome rest. Not a barbiturate, not habit forming, 200 mg induces a sound night's sleep without hangover, or 50 mg t.i.d. provides daytime sedation without somnolence. Noludar tablets, 50 and 200 mg; elixir, 50 mg per teaspoon.

Hoffmann - La Roche Inc.

Nutley 10, New Jersey

Noludar®
brand of methyprylon



Newest in vitamin therapy

Vitamins as nature intended . . .

THE HOMOGENIZED VITAMINS

For the first time, all the advantages of multivitamin drops are available in a tablet. By a unique process, the vitamins are homogenized, then fused into a solid, highly palatable form.

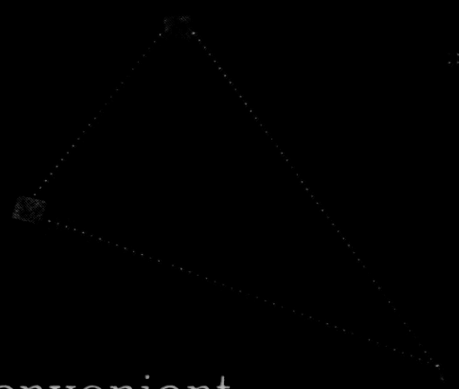
As a result of this minute subdivision, the vitamins are absorbed and utilized much more efficiently than those in the usual compressed tablet or elastic capsule.

- Better absorbed and utilized
- Pleasant, candy-like flavor
- No regurgitation, no "fishy burp"
- May be chewed, swallowed, or dissolved in the mouth

Three formulas:

Prenatal
Pediatric
Therapeutic

The S. E. MASSENGILL COMPANY
Bristol, Tennessee



most convenient

digitalis

preparation . . .

change route

any time

without changing

dose or interval

Now with Digoxine Nativelle Injection . . . range of routes of administration is available . . . tion specifically designed for I.M. use . . . often encountered when I.V. forms are given . . . muscularly. The dosage schedule with NATIVELLE . . . the route of administration . . . vided by oral forms . . . change in therapy . . . NATIVELLE . . . convenient . . . smooth, even . . . unnecessary . . .

Consult your Physicians' Desk Reference . . .

VARICK Pharmaceutical Company, Inc.

75 Varick Street, New York 13, N. Y.

the most potent antipruritic
and anti-inflammatory
agent known
plus antibiotic action against
secondary bacterial
invaders

florinef-S

Squibb Fludrocortisone Acetate with Spectrocin (Squibb Neomycin-Gramicidin)

Florinef-S Lotion (liquid vanishing cream base),
0.05% and 0.1%, 15 ml. plastic squeeze bottles.

Florinef-S Ointment, 0.1%, 5 Gm. and 20 Gm. tubes.

SQUIBB

"FLORINEF"® AND "SPECTROCIN"® ARE SQUIBB TRADEMARKS

for night-long relief of
sleep-disturbing pain

PERSISTIN

6 FLUIDOUNCES
ZIRADRYL
LOTION
for protection from poison ivy and oak and relief of itching in ivy and oak poisoning.
SHAKE WELL BEFORE USING
FOR EXTERNAL USE ONLY
Stock 22-224-39
PARKE, DAVIS & COMPANY
DETROIT, MICHIGAN, U.S.A.

antihistaminic benefits of Benadryl
neutralizing action of zirconium

ZIRADRYL® LOTION

Benadryl® Hydrochloride with Zirconium

an old favorite in a new form

ZIRADRYL Lotion provides the same recognized clinical advantages as **ZIRADRYL** Cream. Antihistaminic-antipruritic properties of Benadryl are combined with the urushiol-neutralizing action of zirconium for effective prevention or treatment of ivy or oak poisoning.

protects against rhus dermatitis

if applied before or soon after exposure.

relieves rhus dermatitis

and reduces spreading if applied after dermatitis appears.

ZIRADRYL Lotion is supplied in 6-ounce bottles.
ZIRADRYL Cream is supplied in 1-ounce tubes.

MEDICAMENTA VERA

PARKE, DAVIS & COMPANY DETROIT, MICHIGAN

50064

microcytic anemia

one of the many anemias which can be effectively treated with

PERIHEMIN*

Hematinic *Lederle*

Nine out of 10 treatable anemias respond to PERIHEMIN. Its potent formula includes every known hemopoietic agent, including Purified Intrinsic Factor Concentrate. With this single product, you provide complete anemia therapy in a form convenient for the patient.

Dosage: one capsule, t.i.d.

Each capsule contains:

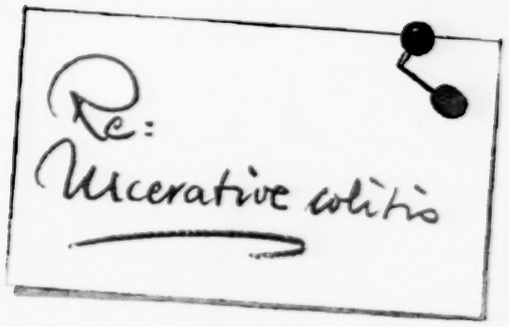
Vitamin B_{12} with Intrinsic Factor Concentrate.. ⅓ U.S.P. Oral Unit
Vitamin B_{12} (additional)... 5 mcgm.
Ferrous Sulfate (Exsiccated). 192 mg.
Folic Acid..... 0.85 mg.
Ascorbic Acid (C)..... 50 mg.
Insoluble Liver Fraction..... 50 mg.

PERIHEMIN JR *Capsules*, for children, are approximately one-quarter the potency of this formula.

dry filled sealed capsules (a Lederle exclusive!) for more rapid and complete absorption!

LEDERLE LABORATORIES DIVISION *AMERICAN Cyanamid COMPANY* PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.

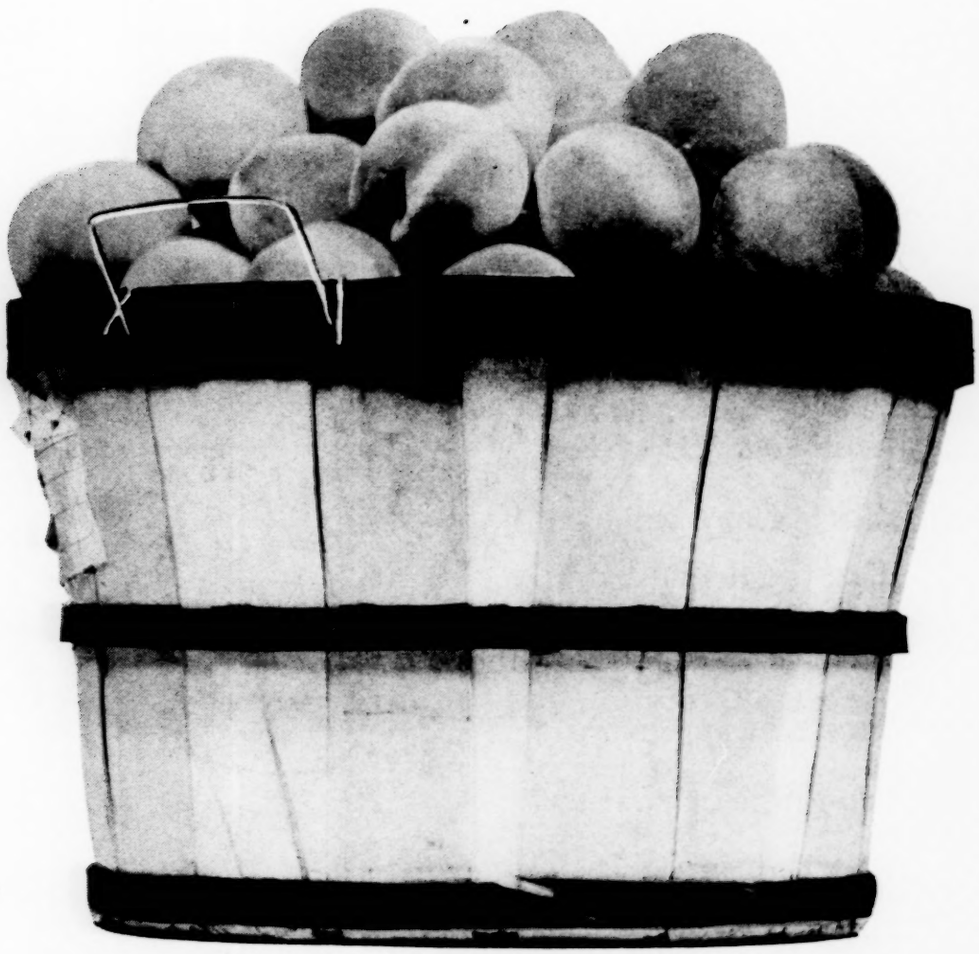


This is "the most valuable drug that has been introduced for the treatment of ulcerative colitis" in recent years.[1] Results of treatment with Azulfidine "far exceed those of any previous drug used".[2] "It has been effective in controlling the disease in approximately two-thirds of patients who had previously failed to respond to standard colitis therapy currently in use."[3]

Azulfidine
BRAND OF SALICYLAZOSULFAPYRIDINE

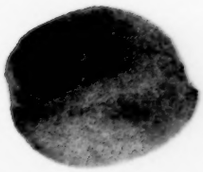
1. BARGEN, J. A.: "Present Status of Hormonal and Drug Therapy of Ulcerative Colitis", South. M. J. *48*: 192 (Feb.) 1955.
2. BARGEN, J. A. and KENNEDY, R. L. J.: "Chronic Ulcerative Colitis in Children", Postgrad. Med. *17*: 127 (Feb.) 1955.
3. MORRISON, L. M.: "Response of Ulcerative Colitis to Therapy with Salicylazosulfapyridine", J. A. M. A. *151*: 366 (Jan. 31) 1953.

PHARMACIA LABORATORIES, INC.
270 Park Avenue, New York 17, N. Y.

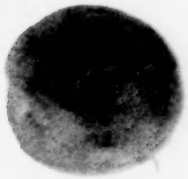


TERRA

BRAND OF OXYTETRACYCLINE



a delightful new taste



in antibiotic therapy...

just like a fresh peach

BON*

HOMOGENIZED MIXTURE

new . . . peach-flavored, peach-colored liquid form of TERRAMYCIN®† 125 mg. oxytetracycline per 5 cc. teaspoonful; bottles of 2 fl. oz. and 1 pint, packaged ready to use.

*Trademark †Brand of oxytetracycline

Pfizer PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.

more **CERTAIN**

CONTROL OF DIARRHEA

(whether toxic, neuromuscular or emotional in origin)

because

more* COMPREHENSIVE *in* *therapeutic effects

- adsorbs toxins
- soothes mucosa
- reduces hyperperistalsis
- neutralizes hyperacidity
- eases emotional tension

DONNAGEL®

Robins

(DONNATAL WITH KAOLIN AND PECTIN COMPOUND)

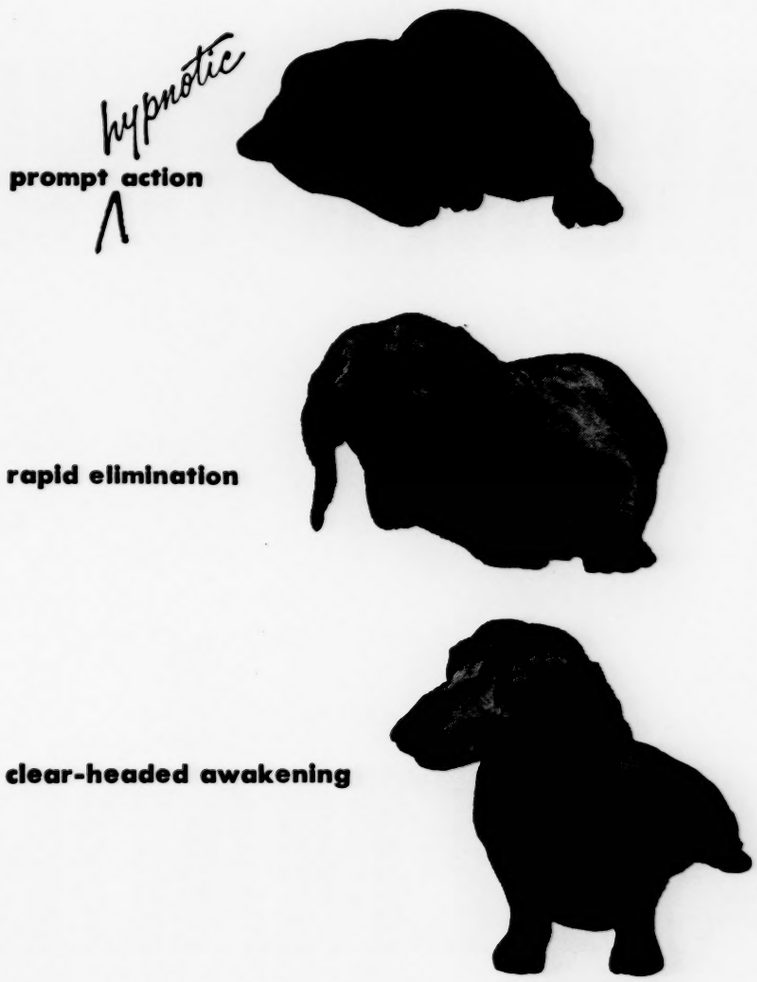
Each 30 cc. of Donnagel contains:

Hyoscyamine Sulfate	0.1037	mg.
Atropine Sulfate	0.0194	mg.
Hyoscine Hydrobromide	0.0065	mg.
Phenobarbital (¼ gr.)	16.2	mg.
Kaolin (90 gr.)	6.0	Gm.
Pectin (2 gr.)	130.0	mg.
Dihydroxy aluminum aminoacetate (7½ gr.)	0.5	Gm.

Robins

A. H. ROBINS CO., INC., RICHMOND 20, VA.

Ethical Pharmaceuticals of Merit since 1878



ELIXIR ALURATE *'Roche'*

Available as ELIXIR ALURATE, cherry red color/ELIXIR ALURATE VERDUM, emerald green color
Each contains 0.03 Gm (½ grain) of Alurate per teaspoonful (4 cc)
in a palatable vehicle. Alurate®—brand of aprobarbital

HOFFMANN-LA ROCHE INC. • ROCHE PARK • NUTLEY 10 • NEW JERSEY

NEW *for those with* PARKINSONISM

Smoother activity

and

brighter expression

with 'KEMADRIN'®*

- reduces rigidity and tremor.
- seldom causes dryness of the mouth, blurring of vision or excitation.

***'KEMADRIN'** brand Procyclidine Hydrochloride
Tablet of 5 mg., scored. Bottles of 100 and 1,000.

Literature available on request.

BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, N.Y.

antihistaminic benefits of Benadryl
neutralizing action of zirconium

ZIRADRYL® LOTION

Benadryl® Hydrochloride with Zirconium

an old favorite in a new form

ZIRADRYL Lotion provides the same recognized clinical advantages as **ZIRADRYL** Cream. Antihistaminic-antipruritic properties of Benadryl are combined with the urushiol-neutralizing action of zirconium for effective prevention or treatment of ivy or oak poisoning.

protects against rhus dermatitis

if applied before or soon after exposure.

relieves rhus dermatitis

and reduces spreading if applied after dermatitis appears.

ZIRADRYL Lotion is supplied in 6-ounce bottles.
ZIRADRYL Cream is supplied in 1-ounce tubes.

MEDICAMENTA VERA

PARKE, DAVIS & COMPANY DETROIT, MICHIGAN

50084

Clinical evidence[1, 2, 3] indicates that to **augment the therapeutic advantages** of Prednisone and Prednisolone, antacids should be **routinely co-administered**

A Multiple Compressed Tablet of 'CO DELTRA' or 'CO HYDELTRA' is specifically designed as a 'tablet within a tablet' to provide stability and to release in sequence, antacid and anti-inflammatory agents:

1. the outer layer of antacids comes in contact with the gastric mucosa first and after it is completely dissolved;
2. the hitherto intact inner core releases the steroid then begins to release its therapeutic potential and not before.

'CO DELTRA' and 'CO HYDELTRA' are trade marks of Merck & Co., Inc.

All the benefits of prednisone and prednisolone:

1. less sodium and water retention.
2. marked anti-inflammatory activity at low dosage.
3. prompt response even in patients refractory to other steroids.

PLUS

A. positive antacid action to minimize gastric distress.

B. full potency and stability.

C. uniform dependable results.

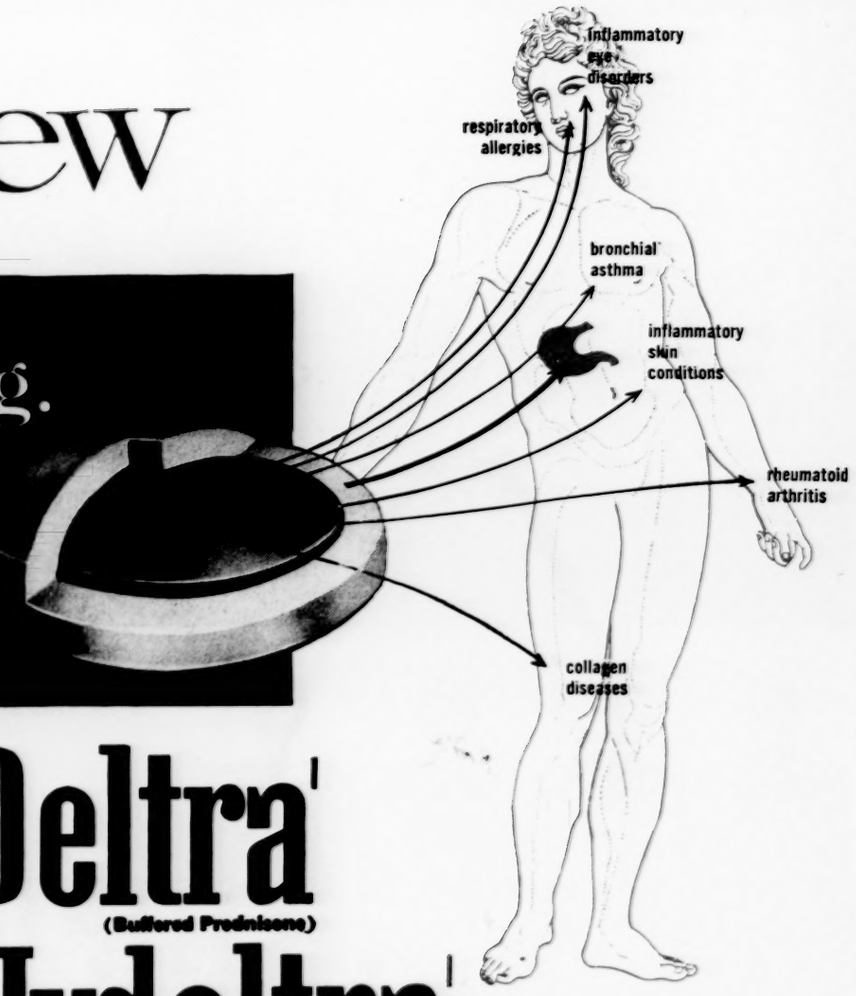
D. greater flexibility of dosage with the addition of the new 2.5 mg. strength.

References: 1. Boland, E. W., *J.A.M.A.* **160**:613, February 25, 1956. 2. Margolis, H. M., *et al. J.A.M.A.* **158**:454, June 11, 1955. 3. Bollet, A. J., *et al. J.A.M.A.* **158**:459, June 11, 1955.

New

2.5 mg.

Multiple Compressed Tablets



'Co-Deltra'
(Buffered Prednisone)

'Co-Hydeltra'
(Buffered Prednisolone)

increase the flexibility of therapy with the "predni-steroids"

All *the benefits of prednisone and prednisolone* plus *greater antacid-to-steroid ratio to minimize gastric distress during maintenance therapy.*

The new 2.5 mg. tablets of 'CO-DELTRA' and 'CO-HYDELTRA' together with the 5 mg. tablets give the physician more latitude for precise adjustment of dosage to the individual patient's needs. Cost for either strength tablet is substantially the same as for the steroid alone and in addition the multiple compressed tablets assure routine co-administration of both antacid and steroid components..

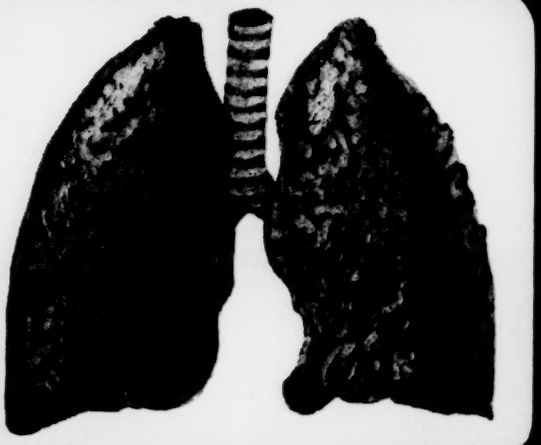
Supplied: 'CO-DELTRA' (Prednisone Buffered) and 'CO-HYDELTRA' (Prednisolone Buffered) are available as Multiple Compressed Tablets, each tablet containing 2.5 mg. or 5 mg. of prednisone or prednisolone plus 300 mg. of dried aluminum hydroxide gel, and 50 mg. of magnesium trisilicate.

SHARP & DOHME

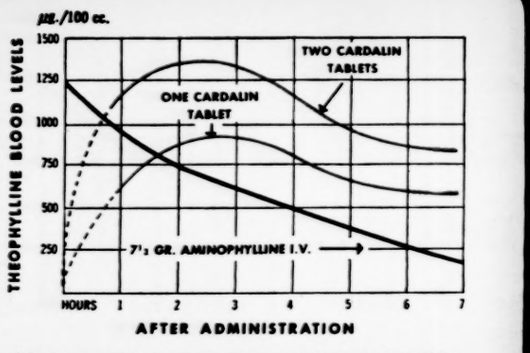
Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

FIRST SHOWING...

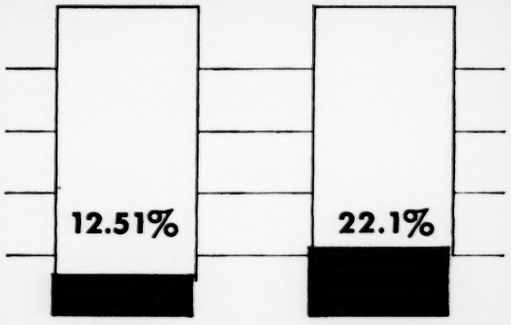
"A NEW CONCEPT IN ASTHMA CONTROL"



2. Cardalin (protected aminophylline) can make therapy safer in severe asthma.



(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11: 301, 1953, and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100: 309, 1950.)



5. Cardalin works by producing high, sustained theophylline blood levels within an hour,

6. thereby increasing the asthmatic's vital capacity and maximum breathing capacity.

Concurrent therapy with CARDALIN can minimize these risks of corticoid therapy:

- **activation and perforation of gastric ulcers**
- **water and salt retention**
- **nervous tension and undue mental stimulation**

3. Concurrent therapy with Cardalin can reduce the effective dose of corticoids, avoid overdosage effects . . .

4. and lead to: safer control of asthma • quicker remissions • fewer side effects • faster discontinuance of corticoids and less costly treatment.

How Cardalin can reduce dosage of corticoids

1 Begin with prednisone*—15 mg. q.i.d. and 1 Cardalin tablet before breakfast, at 4 p.m. and at bedtime.

2 After severe symptoms are relieved (2nd or 3rd day) reduce the dose of prednisone* to 10 mg. q.i.d.; continue Cardalin dosage.

3 After remission occurs (slight or no asthma) reduce the dose of prednisone to 5 mg. q.i.d.; give 1 Cardalin tablet morning and at bedtime.

Reduce prednisone dosage 5 mg. each week, attempting to discontinue its use. Continue Cardalin at reduced dosage level (1 tablet, morning and at bedtime).

*or any corticoid of your choice, in appropriate dosage.

℞ Cardalin TABLETS

Each tablet contains:

Aminophylline	5.0 gr.
Aluminum hydroxide	2.5 gr.
Ethyl aminobenzoate	0.5 gr.

Also available, Cardalin-Phen, containing in addition, ¼ gr. phenobarbital per tablet.

You can give a full therapeutic dose of aminophylline orally with Cardalin tablets. Two protective factors—aluminum hydroxide and ethyl aminobenzoate—effectively minimize gastric irritation so common with other forms of aminophylline, and also with corticoids.

7. As a result, a smaller amount of corticoids need be given and asthma therapy is made safer and more economical.

8. Look for further details in your mail this month!

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

through-the-night photographs show...

NONBARBITURATE

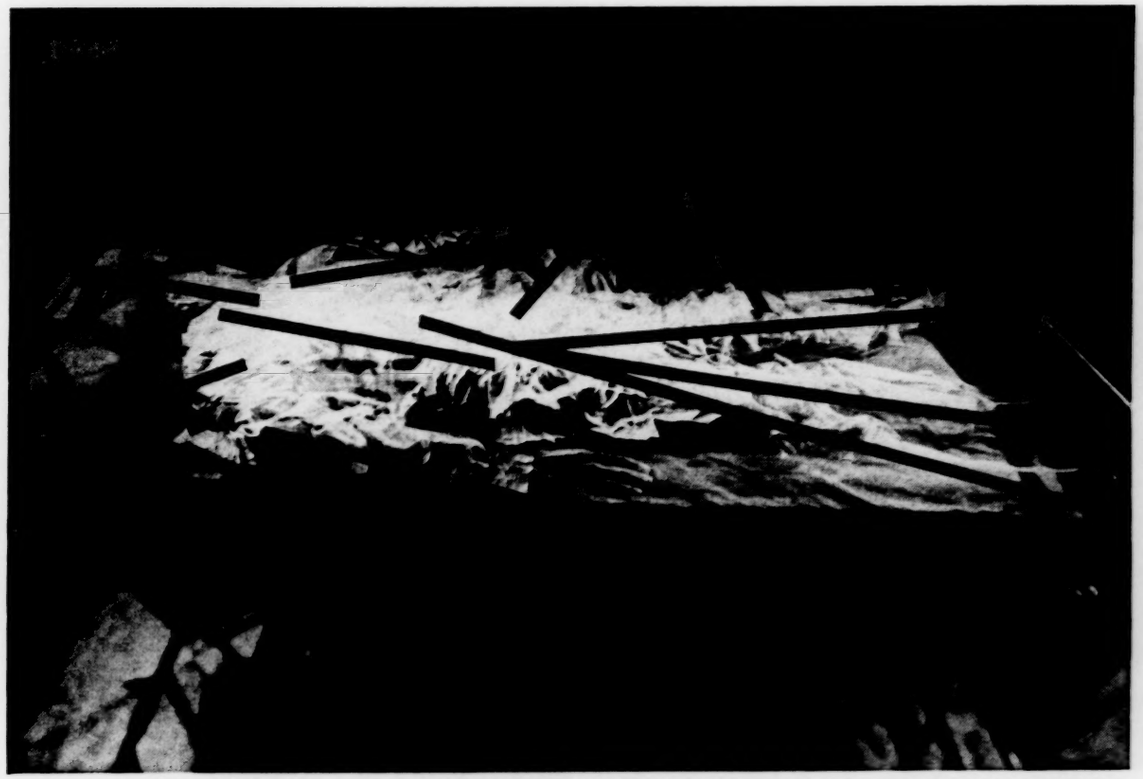
Doriden®

Habituation has not been reported

Twenty-eight-year-old male, restless sleeper, tense personality with occasional insomnia, was photographed at fixed intervals during the night to produce a series of exposures on same sheet of film. On placebo (above), unique "stroboscopic" picture shows him in typical fitful night of unrest.

Further clinical evidence of the sedative and hypnotic effectiveness of DORIDEN is provided by numerous clinical studies. In most cases, Doriden acts in 15 to 30 minutes, affords 4 to 8 hours of refreshing sleep... and come morning, the patient awakens "clear-headed."

induces sound, restful sleep



Same patient on successive night, following administration of Doriden 0.5 Gm. at bedtime, is shown in distinctly more restful repose. Total sleep was achieved in 16 minutes. Close study of activity pattern shows approximately 50 per cent reduction in overt motion and restlessness.

DORIDEN is also an excellent daytime sedative... calms the tense, anxious, overwrought patient.

DOSAGE: For SLEEP—0.5 Gm. at bedtime.
As a DAYTIME SEDATIVE—0.125 or 0.25 Gm. t.i.d. after meals.

TABLETS, 0.125 Gm., 0.25 Gm. (scored) and 0.5 Gm. (scored).

DORIDEN® (glutethimide CIBA)

CIBA
SUMMIT, N. J.

2/2213M

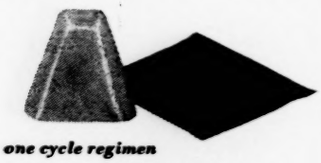
89.9% *of patients free from trichomoniasis in one menstrual cycle*

This receptionist's symptoms of local itching and burning are gone, due to her doctor's thorough powder insufflation and her own use of suppositories at home.

- *many cases refractory* to previous therapies responded to TRICOFURON *combined* therapy in 4 clinical studies of 108 patients.* Cure rate was 89.9%. Recurrences were few
- *advantages:* contains a specific, trichomonacidal nitrofuran. Kills many secondary invaders but permits essential Döderlein's bacillus to exist. Effective in blood, pus and vaginal debris
- *office treatment:* insufflate TRICOFURON Powder twice the first week and once a week thereafter
- *home treatment:* first week—the patient inserts one TRICOFURON Suppository each morning and one each night at bedtime. Thereafter: one a day—a second if needed—to maintain trichomonacidal action

Suppositories contain 0.25% Furoxone® (brand of furazolidone) in a water-miscible base. Hermetically sealed in green foil. Box of 12. Powder contains 0.1% Furoxone in water-miscible base composed of lactose, dextrose and citric acid. Bottle of 30 Gm.

***Personal Communications to Medical Department, Eaton Laboratories. Detailed information available on request.**



one cycle regimen

TRICO

EATON LABORATORIES, Norwich, N.Y. NITROFURANS

antihistaminic benefits of Benadryl
neutralizing action of zirconium

ZIRADRYL® LOTION

Benadryl® Hydrochloride with Zirconium

an old favorite in a new form

ZIRADRYL Lotion provides the same recognized clinical advantages as **ZIRADRYL** Cream. Antihistaminic-antipruritic properties of Benadryl are combined with the urushiol-neutralizing action of zirconium for effective prevention or treatment of ivy or oak poisoning.

protects against rhus dermatitis

if applied before or soon after exposure.

relieves rhus dermatitis

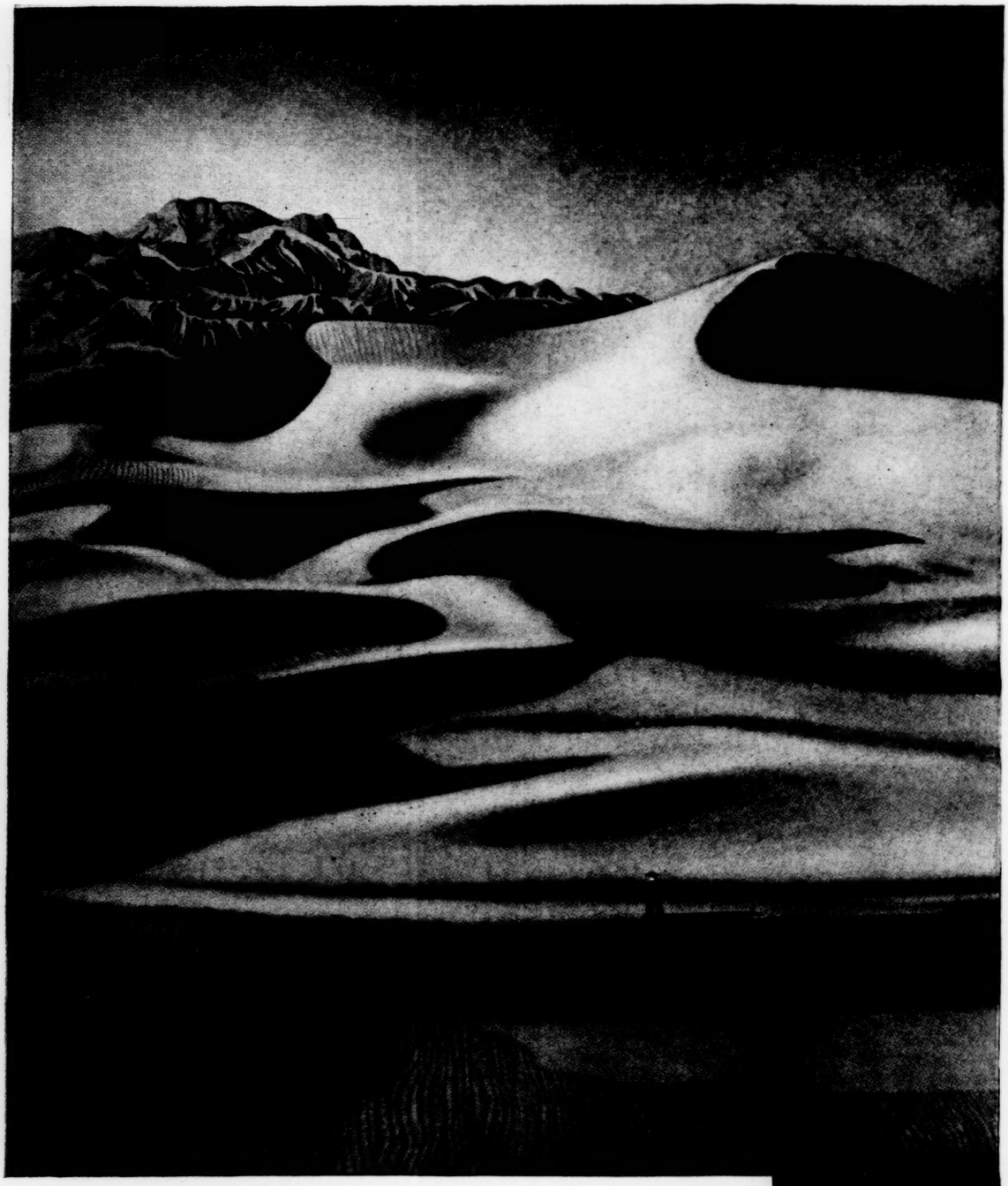
and reduces spreading if applied after dermatitis appears.

ZIRADRYL Lotion is supplied in 6-ounce bottles.
ZIRADRYL Cream is supplied in 1-ounce tubes.

MEDICAMENTA VERA

PARKE, DAVIS & COMPANY DETROIT, MICHIGAN

50084



escape

Betasyamine® . . . for an escape from fatigue . . . in your aging patients.

Betasyamine carries its therapeutic attack to the very source of a basic biochemical inadequacy, typical of your chronically fatigued and tense aging patients.

Carlson[1] associates the aging process with progressively impaired neuromuscular function; Dixon[2] links this decline with chronic tension and fatigue brought about by depleted values of phosphocreatine. Betasyamine is not a sedative, not a stimulant drug. It is true replacement therapy. Betasyamine, containing betaine and glycocyamine, precursors of phosphocreatine, serves to replenish these vital stores to optimal levels needed for vigorous body functioning. In this manner, Betasyamine re-energizes the tense, exhausted patient. By its purely physiologic action, Betasyamine offers a new-found means to meet the problem of autumnal years, whether they be environmental, physical, emotional.

With Betasyamine, escape from fatigue in aging patients is achieved; a new will to keep going, stronger than ever.

Average Dosage: 1 Effervescent Packet; 1 tablespoonful Emulsion; or 5 Tablets three times daily at mealtimes.

Supplied: Effervescent Packets (New) — 24's; Emulsion — 16 fl. oz.; Tablets — 200's.

References: 1. Carlson, A. J., in Stieglitz, E. J.: Geriatric Medicine, ed. 3, Philadelphia, J. B. Lippincott Company, 1954, p. 71. • 2. Dixon, H. H.; Peterson, R. D.; Dickel, H. A.; Jones, C. H., and West, E. S.: West J. Surg. *60*:327 (July) 1952.

Amino Products Division • International Minerals & Chemical Corporation
Chicago • San Francisco • Los Angeles

escape escape

ACHROMYCIN

Tetracycline *Lederle*

in the treatment of

infections in surgery

The prevention and control of cellulitis, abscess formation, and generalized sepsis has become commonplace technique in surgery since ACHROMYCIN has been available. Leading investigators have documented such findings in the literature.

For example, Albertson and Trout[1] have reported successful results with tetracycline (ACHROMYCIN) in diverticulitis, gangrene of the gall bladder, tubo-ovarian abscess, and retropharyngeal abscess. Prigot and his associates[2] used tetracycline in successfully treating patients with subcutaneous abscesses, cellulitis, carbuncles, infected lacerations, and other conditions.

As a prophylactic and as a therapeutic, ACHROMYCIN has shown its great worth to surgeons, as well as to internists, obstetricians, and physicians in every branch of medicine. This modern antibiotic offers rapid diffusion and penetration, quick development of effective blood levels, prompt control over a wide range of organisms, minimal side effects. There are 21 dosage forms to suit every need, every patient, including

ACHROMYCIN SF

ACHROMYCIN with STRESS FORMULA VITAMINS. Broad-range antibiotic action to fight infection; important vitamins to help speed normal recovery. In *dry-filled, sealed* capsules for rapid and complete absorption, elimination of aftertaste.

[1]Albertson, H.A. and Trout, H. H., Jr.: *Antibiotics Annual* 1954-55, Medical Encyclopedia, Inc., New York, N.Y., 1955, pp. 599-602.

[2]Prigot, A.; Whitaker, J. C.; Shidlovsky, B. A., and Marmell, M.: *ibid*, pp. 603-607.

Lederle

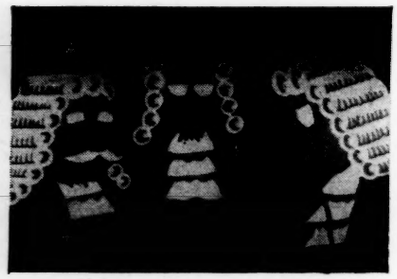
LEDERLE LABORATORIES DIVISION

AMERICAN CYANAMID COMPANY

PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.

PHOTO DATA: AERIAL CAMERA WITH K-2 FILTER AT DUSK, F.11, 4/100 SEC., FAST PAN FILM



a "judicious combination..."

for antiarthritic therapy

SALCORT*

That cortisone and the salicylates have a complementary action has been well established.[1-5] In rheumatic conditions, functional improvement and a sense of feeling well are noted early. No withdrawal reactions have been reported.

One clinician states: "By a judicious combination of the two agents . . . it has been possible to bring about a much more favorable reaction in arthritis than with either alone. Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."[1]

INDICATIONS:

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Bursitis . . . Still's disease . . . Neuromuscular affections

EACH TABLET CONTAINS:

Cortisone acetate	2.5 mg.
Sodium salicylate	0.3 Gm.
Aluminum hydroxide gel, dried .	0.12 Gm.
Calcium ascorbate	60 mg.
(equivalent to 50 mg. ascorbic acid)	
Calcium carbonate	60 mg.

* U.S. Pat. 2,691,662

1. Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105 (Nov., 1955).
2. Roskam, J., VanCawenberge, H.: Abst. in J.A.M.A., 151:248 (1953).
3. Coventry, M.D.: Proc. Staff Meet., Mayo Clinic, 29:60 (1954).
4. Holt, K.S., et al.: Lancet, 2:1144 (1954).
5. Spies, T.D., et al.: J.A.M.A., 159:645 (Oct. 15, 1955).

BRISTOL, TENNESSEE
NEW YORK
KANSAS CITY
SAN FRANCISCO

The S. E. Massengill company

When summer drinks bring diarrhea...

Cremosuxidine®

SULFASUXIDINE® SUSPENSION WITH PECTIN AND KAOLIN

MAJOR ADVANTAGES: Has pronounced antibacterial action. Detoxifies and adsorbs intestinal irritants. Soothes the mucosa. Tasty chocolate-mint flavor.

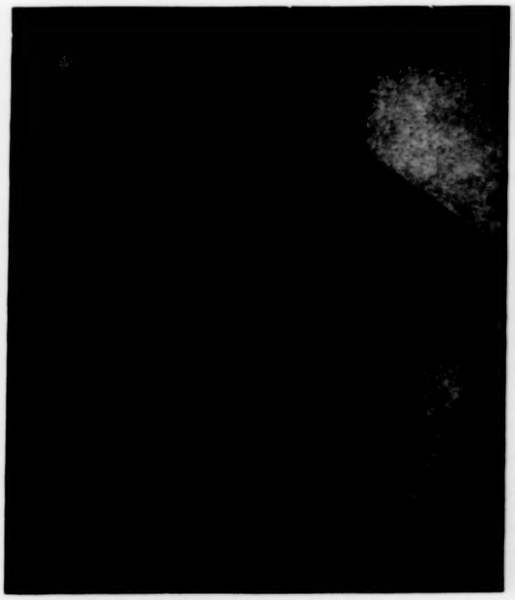
Adult dosage: 1½ to 2 tbsp. six times a day. *Children and infants* in proportion.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF
MERCK & CO., INC.

Back Issues Wanted

(MUST BE IN GOOD CONDITION)



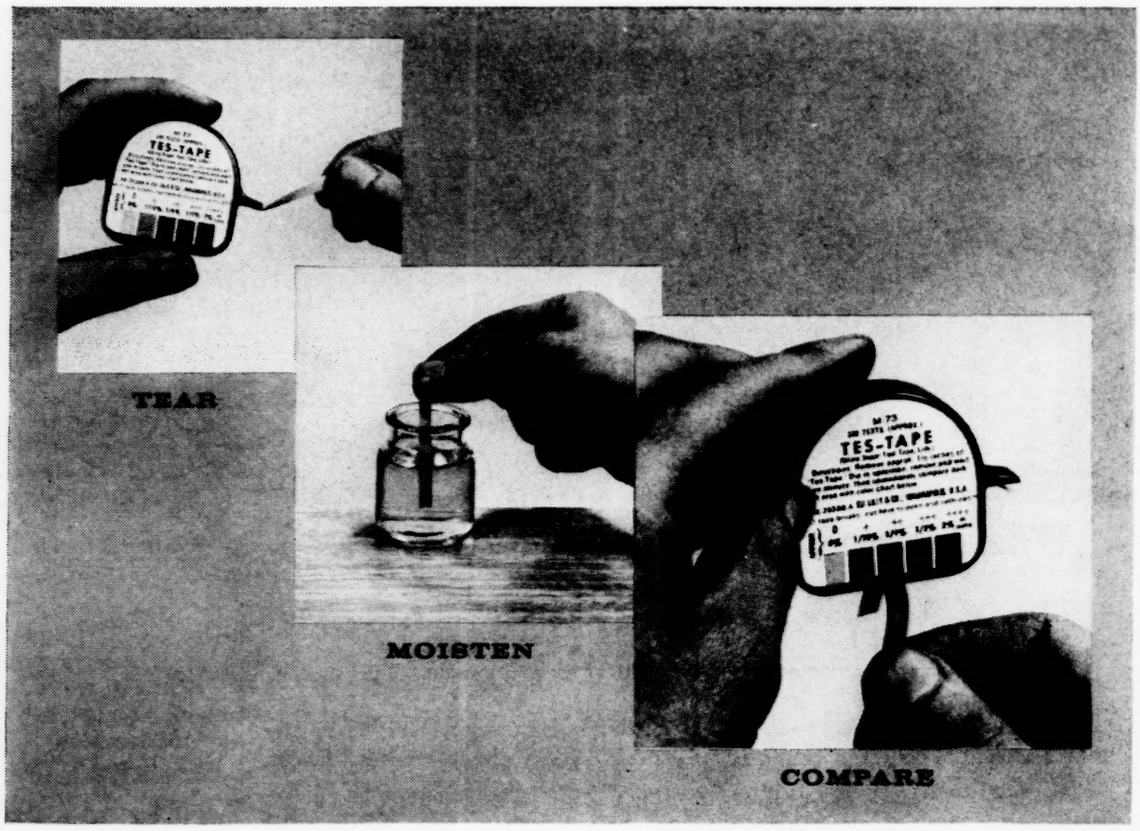
THE AMERICAN JOURNAL OF MEDICINE

will pay $1.00 per copy for the following issues:

January 1948	December 1954
March 1948	May 1955
July 1948	August 1955
September 1948	September 1955
February 1953	October 1955

Send to

The American Journal of Medicine, Inc.
49 West 45th Street New York 36, N. Y.



626061

NEW

urine sugar test of unmatched simplicity

'Tes-Tape'

(URINE SUGAR TEST TAPE, LILLY

'Tes-Tape' completely eliminates the need for test tubes, heat, reagents, or any other paraphernalia in quantitative urine sugar determinations. Simply moisten a strip of 'Tes-Tape' with the specimen. After just sixty seconds, compare it with the color chart on the 'Tes-Tape' dispenser. Then read off the percentage of sugar. The selective action of 'Tes-Tape' prevents false positive reactions, assures complete accuracy.

The convenient size of the 'Tes-Tape' dispenser permits you to carry it on house calls for on-the-spot determinations. Your patients also will welcome the convenience, simplicity, and accuracy of 'Tes-Tape.'

Now available at pharmacies everywhere.

Lilly

QUALITY / RESEARCH / INTEGRITY

80TH ANNIVERSARY 1876 · 1956 / ELI LILLY AND COMPANY

The American Journal of Medicine

VOL. XX JUNE, 1956 No. 6

Editorial

The Levels of Disorganization

To the physiologic chemist the human or other animal is a complex integrated mass of chemical substances and chemical reactions. Confronted with the task of trying to understand and explain the functioning of the animal in chemical terms, the investigator is prone to attack the problem analytically, to dissect one organ from another, to separate one compound or group of compounds from another. By such devices he hopes to attain a less complex part of the whole which is more likely to be susceptible to study, to comprehension.

In laboratory jargon, reference is often made to the "level of organization" of the biologic system under study. It appears to us that this designation places the emphasis improperly. The investigator, in his experiments, rarely if ever organizes; rather, he disintegrates or disorganizes what was in nature highly integrated and organized. For this reason we have preferred to consider the "levels of *dis*organization"[1] at which the biochemist may study the nature of chemical processes in biologic systems. As we proceed through these several levels—the more or less intact animal, the isolated perfused organ, the sliced or minced tissue, the morphologically recognizable subcellular particle, the purified enzyme—at each successive step certain definite and obvious advantages accrue to the investigator. Equally obvious but more frequently overlooked are the disadvantages, from the viewpoint of understanding of the whole, which result from this process of dissection and chemical degradation.

In dealing with the intact animal difficulties arise from the complexity of the system, and limitations are imposed upon the independent variables at the command of the experimenter. He can control the composition and pressure of the gaseous environment, the ambient temperature, the quantity and composition of the diet and the amount of muscle work. Other than indirectly he cannot control the detailed composition of the circulating fluid. The number of useful procedures available to him is limited. He may study the effects of the several controllable variables on the composition of tissues and excreta, or he may measure certain physiologic functions as they are affected by these variables. A peculiarly useful special case is the measurement of the distribution of isotope after administration to the intact animal of an isotopic compound. While information derived from the study of the intact animal may be in a sense superficial, it has at least the mark of authenticity. "The proper science and subject for man's contemplation is man himself."

How to disintegrate this complex organism to render it more approachable by the experimental method? We excise an organ, establish a fistulous tract or otherwise operate upon our animal. It is now something less than an intact animal but still it is probable that what is observed to happen in such a postoperative preparation is reasonably close to what may happen in a normal counterpart. In the totally eviscerated animal the resemblance is more remote and from here it is only a step to the combined organ systems dear to the classic physiologist, the heart-lung preparation, the nerve-muscle preparation. The next level is that of the isolated perfused organ.

We may profitably consider what has been gained, and what lost, by the disorganization thus far described. In working with the perfused

[1] WHITE, A., HANDLER, P., SMITH, E. L. and STETTEN, D., JR. Principles of Biochemistry, pp. 289–293. New York, 1954. McGraw-Hill Book Co., Inc.

organ the experimenter has gained complete control, within limits, of the composition and pressure of the perfusing fluid. He has also acquired access, for analytic study, to the discharged perfusate. The organ under study has been divorced, however, from all other organs, and insofar as it is normally subject to humoral or neural influences, these have now been abolished. Humoral influences include variations in concentration of endocrines and nutrients arising in remote tissues; neural influences may be exerted not only on the organ proper but also on its vascular supply. Most of the known homeostatic mechanisms, involving negative feed-back from one organ to another, are also lost when an organ is isolated.

Having removed the organ or tissue from its normal habitat, the experimenter may next elect to slice it or, if this is impractical, to mince it. Such biochemical butchery is intended to increase the surface-to-volume ratio to permit adequate nutrition and oxygenation of tissue to proceed from the suspending medium. Whereas this technic gives the experimenter complete control over the composition of the gas and liquid phases, it suffers from serious drawbacks. Inevitably some cells will have been ruptured in the process, permitting spillage of intracellular contents. Only the most wildly optimistic worker will consider that the cells of the liver are normally nourished when slices thereof, many cells in thickness, are sloshing in a leisurely fashion in a Warburg vessel. This situation is to be contrasted with that of the polygonal cells of the liver *in situ*, each of which is in contact with a venous sinus through which blood rapidly courses. In the sliced or minced tissue, nutrients are inadequately delivered, wastes are inadequately removed. Unless special precautions are taken substrates in the medium decrease, while products of cellular metabolism increase in concentration with the passage of time, a situation which has no counterpart in the tissues of the normal balanced animal.

If the tissue is homogenized so as to rupture cell membranes, the experimenter may investigate a number of important questions not susceptible to study at less disorganized levels. Enzymes are either solubilized or, if insoluble, may be assigned to one or another subcellular particle species, i.e., nucleus, mitochondrion or microsome. Free access to intracellular enzyme is assured for test substrates which may be insulated from the intracellular enzymes by an intact cell wall. What has been lost, however, is not inconsiderable. The anatomic relationships within the cell, which must have biochemical significance, have been destroyed. The loss of the discriminating function of the cell membrane, which normally serves to separate many extra- from intracellular materials may lead to false positive findings, the discovery of enzyme-catalyzed reactions which cannot occur in the intact animal because substrate and enzyme are separated from each other by a membrane. Some degree of cellular organization may prove to be an absolute requirement for the study of certain biochemical events, and it may be noted that to date no entirely satisfactory evidence has been presented for the occurrence of an endocrinologic effect if the effector tissue has been homogenized.

The final step in disorganization, which is in a sense the culmination of the efforts of the enzyme chemist, is the purification and crystallization of an enzyme. This permits determination of the thermodynamic and kinetic constants of the enzyme-catalyzed reaction, elucidation of cofactor requirements and of inhibitors, and study of substrate specificity and of intimate reaction mechanism. This last step in the disintegration process, like those which have gone before, results in the loss of certain of the attributes of biochemical processes as they occur *in vivo*. Other molecular species which, in the cell, may enhance or inhibit the activity of an enzyme are necessarily lost when the enzyme is purified. In the cell, the product of one reaction is in general the precursor of another, the energy yielded by one process is consumed by another. In the course of isolation of a given enzyme-catalyzed reaction, these important relationships are lost.

Which of these many levels of disorganization is then to be recommended? The answer to this question is that unequivocal results as to what is happening in the intact mammal cannot be gleaned from studies conducted at any one level. Each level, considered separately, has led to unsatisfactory conclusions. We know of reactions catalyzed by isolated enzymes for which no counterpart in the intact animal has been discovered. We know of over-all conversions observed in the intact animal which have thus far defied study at subcellular levels and for which no enzymes have been unearthed. It is improper to hold that any one approach is in all cases superior to all others. Selection of level of

disorganization, often in fact determined by the skills or prejudices of the individual investigator, should be based upon the nature of the specific question which is being asked. When results secured at several or all levels of disorganization are concordant with one hypothesis, only then is it safe to conclude that a biologic truth has been established.

DeWitt Stetten, Jr., M.D.
National Institute of Arthritis and Metabolic Diseases, Bethesda, Md.

Clinicial Studies

Studies on Myocardial Metabolism*

VI. Myocardial Metabolism in Congestive Failure

J. M. Blain, M.D., H. Schafer, M.D., A. L. Siegel, M.S. *and* R. J. Bing, M.D.
Birmingham, Alabama

Accumulation of information regarding the metabolic processes in the heart muscle of human subjects with congestive heart failure has been hampered by lack of suitable technics for studying the problem in the environment under which it develops and in which it continues to progress. Most previous studies of the metabolism of the failing heart have utilized either the isolated mammalian heart-lung preparation, a pump-oxygenator system or, more recently, intubation of the coronary sinus. While extremely valuable, the information obtained by such methods is not necessarily applicable to human congestive heart failure, or at least is subject to considerable misinterpretation when analogies are attempted.

Demonstration that catheterization of the coronary sinus can be carried out in the human subject without danger has provided a means not only of gathering data which would otherwise be unobtainable but also of conducting appropriate studies under physiologic conditions with normally operating nervous and hormonal regulatory mechanisms.[1] Despite certain inherent limitations, catheterization of the coronary sinus, since applicable to human subjects, is of particular value in the study of congestive heart failure, a disorder which cannot reliably be reproduced in experimental animals.[2] Complete descriptions of the technic can be found elsewhere.[1,3,4] The basis for its application to studies of the type described in this report is briefly presented here.

Since the coronary sinus is the venous outflow system for blood which has perfused the left ventricle predominantly, simultaneous sampling of coronary sinus and peripheral arterial blood permits calculation of the myocardial arteriovenous differences of blood gases, foodstuffs or other constituents.[5] By concomitant measurement of coronary flow using the nitrous oxide technic, a reasonably accurate calculation can be made of the weight or volume of material extracted from or added to the coronary circulation by a given weight of perfused left ventricle.[6,7] While the net myocardial gain or loss can be determined thereby, the method gives no direct knowledge of the intermediary processes.[2] For example, the pyruvate in coronary sinus blood cannot be considered merely as the unused portion of the pyruvate which entered via the arterial system, since varying portions will probably have been derived from breakdown of other foodstuffs. Unless special technics are employed, such as the use of radioactively labeled substrates, the exact derivation of the venous content cannot be determined, nor can the metabolic pathway of the substrate entering the coronary arterial system be followed. Despite this limitation, the emergence of a spectrum of changes which deviates from the normal pattern may give indirect evidence by means of which the intermediary processes causing the changes may be deduced.

Previous reports of this series have been concerned chiefly with the metabolism of carbohydrate and non-carbohydrate foodstuffs by the human heart in subjects without congestive heart failure.[8–10] It has been shown that under normal resting conditions the myocardium extracts significant amounts of glucose, pyruvate, lactate, fatty acids, amino acids and ketones from coronary blood, and that the extent of extraction of each foodstuff is dependent chiefly

* From the Departments of Medicine and Physiology, The Medical College of Alabama, Birmingham, Alabama.
Work supported by a U. S. Public Health Service Grant No. H-1129(C3), The Life Insurance Medical Research Fund, the American Heart Association and Sandoz Pharmaceuticals.

upon its arterial concentration. In the post-absorptive state the heart derives on the average about 70 per cent of its energy requirements from non-carbohydrate material, chiefly fatty acids, but also amino acids and ketones. When, on the other hand, arterial carbohydrate levels are elevated, 80 or 90 per cent of oxidative needs may be supplied by carbohydrates. The ability of normal heart muscle to utilize whatever foodstuff is supplied can be demonstrated by raising the blood concentration of an individual substrate and observing the consequent increase in myocardial extraction. Experiments in this laboratory have shown, for example, that following the infusion of glucose or amino acids, or ingestion of a fat emulsion, the heart responds by extracting larger amounts of these substances, in many cases in excess of the immediate energy requirements.[8,9]

Considerably less is known about substrate utilization in congestive heart failure. Goodale, Olson and Hackel studied the average myocardial carbohydrate arteriovenous difference in three non-fasting patients with low output failure due to multivalvular disease and reported that no significant variation in the extraction of glucose, lactate or pyruvate could be demonstrated in comparison with nine normal subjects.[11] Bing and coworkers reported similar findings in four subjects with low output failure due to hypertension or rheumatic heart disease.[8] Except for the data from six patients of the present series described in a recent review of the subject of myocardial metabolism, no information is available concerning the pattern of protein and fat utilization by the intact human heart in congestive failure.[2]

One disadvantage of the technic used in these studies is that the extraction of any one foodstuff shows considerable variation from person to person and even in the same subject from minute to minute. Therefore, in order to arrive at statistically reliable conclusions it is necessary to have a series large enough to mitigate the effect of considerable scatter of the individual observations. In view of these considerations the present study was undertaken to provide statistically valid data which could be used to aid in resolving the following problems: (1) Is there any difference in the amount of oxygen consumed by equal weights of normal and failing human heart muscle? (2) Is the failing heart deficient in its ability to utilize any of the basic foodstuffs consumed by the normal heart? (3) Is there any evidence of anaerobic myocardial metabolism in congestive heart failure? (4) Is the reduced efficiency of the failing heart due to deficient energy production or to inefficient energy utilization?

To accomplish this purpose the results obtained by catheterization of the coronary sinus in twenty patients with congestive heart failure of the common etiologies will be presented. The data will be compared with similar findings in two control groups, one consisting of subjects with entirely normal hearts, the other of patients with known heart disease but without congestive failure.

MATERIALS AND METHODS

Since the purpose of the experiment was to study the metabolism of the myocardium in chronic low output congestive heart failure in comparison to subjects without failure, experimental methods and criteria for selection of patients were designed to eliminate other variables as much as possible.

Selection of Patients. As finally constituted, the present series consists of forty-six patients from whom technically satisfactory data were obtained by means of coronary sinus catheterization. These patients, on the basis of the clinical and laboratory findings, were divided into three groups.

Group I is composed of eleven subjects without heart disease. (Table I.) Most were hospitalized patients who had undergone diagnostic study or treatment for a non-cardiac disorder. Three patients (E. E., C. H., A. R.) had diseases which sometimes affect the heart but there was no evidence of cardiac involvement in these particular persons.

Group II consists of fifteen patients with known heart disease but without signs or symptoms of congestive failure at the time of study or at any time in the past. (Table II.) Seven of these patients had hypertensive or hypertensive and arteriosclerotic heart disease. Inactive rheumatic heart disease with multivalvular involvement was present in two patients, and was perhaps also present in one of the hypertensives (patient J. J.). Enlargement of the right ventricle due to pulmonary emphysema was present in two. One had aortic insufficiency due to syphilis and the remaining three had non-cyanotic congenital heart disease. Although three of the patients (W. H., E. E., C. I.) in this group were moderately anemic, all had 10 gm. or more of hemoglobin. The increased cardiac index in one subject (E. E.) was attributed to anemia.

Group III is comprised of twenty patients with low output failure. (Table III.) The etiologic diagnoses and number of cases of each were as follows: hypertensive, eight; rheumatic heart disease, four; hypertensive and arteriosclerotic, one; arteriosclerotic, one; chronic glomerulonephritis, one; polycystic renal disease and hypertension, one; senile heart disease, one; con-

TABLE I

Patients	Age (yr.)	Diagnosis	Cardiac Index (L./M²/m.)	R.Q. of Heart	Coronary Flow (cc./100 gm./min.)	Arterial Levels and Myocardial: Δ Oxygen (vol. %)	Arterial Glucose (mg./100 cc.)	Δ Glucose	Arterial Pyruvate (mg./100 cc.)	Δ Pyruvate	Arterial Lactate (mg./100 cc.)	Δ Lactate	Arterial Fatty Acids (mEq./100 cc.)	Δ Fatty Acids	Arterial Amino Acids (mg. N/100 cc.)
1. H. W.	44	Normal	3.83	0.95	...	10.2	110.5	2.0	1.020	0.080	7.60	0.30	1.760	0.015	.....
2. E. E.	23	Essential hypertension; no symptoms, no cardiac enlargement	5.62	0.68	88	11.0	89.1	1.8	0.592	0.000	5.13	1.63	0.870	0.044	3.58
3. T. G.	40	Normal	3.00	0.73	87	9.6	87.5	4.8	0.440	0.000	6.41	2.30	1.045	0.005	4.65
4. J. A.	63	Norma	3.19	0.69	109	8.8	93.6	6.0	0.392	0.036	4.56	0.65	0.930	0.015	3.70
5. E. S.	53	Normal	2.97	0.93	...	11.2	114.1	6.1	0.515	0.048	7.11	0.87	1.253	0.018	3.74
6. C. H.	44	Sarcoidosis, normal heart	.....	0.64	95	9.9	92.0	3.0	0.596	0.175	8.85	1.00	1.270	0.020	3.25
7. J. D.	39	Normal	3.08	0.74	...	9.3	72.9	0.9	0.389	0.018	6.13	1.46	1.160	0.020	3.95
8. D. A.	53	Normal	4.47	0.72	...	12.6	90.2	4.8	0.376	0.019	8.10	4.03	1.135	0.008	4.40
9. T. E.	18	Normal	4.44	0.54	...	10.3	101.1	3.3	0.365	0.125	4.92	1.11	0.880	0	4.75
10. A. R.	21	Rheumatoid arthritis; normal heart	4.23	1.00	...	9.6	85.0	0.4	0.727	0.184	7.25	2.17	0.920	0.043	.....
11. J. W.	68	Normal	3.20	0.64	66	12.0	90.0	0.8	0.388	0.008	6.09	0.67	1.410	0.015	4.35
		Range	3.00 to 5.62	0.54 to 1.00	66 to 109	8.8 to 12.6	72.9 to 114.1	0.4 to 6.1	0.365 to 1.020	0.0 to 0.184	4.56 to 8.85	0.30 to 4.03	0.870 to 1.760	0.0 to 0.044	3.25 to 4.75
		Mean	3.803	0.751	89	10.409	93.27	3.082	0.527	0.0630	6.504	1.472	1.148	0.0184	4.041

TABLE II

Patients	Age (yr.)	Diagnosis	Cardiac Index (L./M²/m.)	R.Q. of Heart	Coronary Flow (cc./100 gm./min.)	Arterial Levels and Myocardial: Δ Oxygen (vol. %)	Arterial Glucose (mg./100 cc.)	Δ Glucose	Arterial Pyruvate (mg./100 cc.)	Δ Pyruvate	Arterial Lactate (mg./100 cc.)	Δ Lactate	Arterial Fatty Acids (mEq./100 cc.)	Δ Fatty Acids	Arterial Amino Acids (mg. N/100 cc.)
1. W. H.	47	H.C.V.D., severe anemia	3.05	0.57	113	7.9	96.1	5.6	0.412	0.054	4.44	0.73	1.210	0.020	3.72
2. G. G.	48	H.C.V.D.	3.17	0.77	71	12.6	89.1	4.7	0.525	0.070	7.94	2.01	1.350	0	3.76
3. E. E.	36	H.C.V.D., anemia	5.99	0.76	112	10.2	95.6	2.1	0.788	0.105	7.67	0.52	1.580	0.015	4.65
4. D. T.	37	R.H.D. with aortic stenosis and insufficiency	2.15	0.82	98	14.9	82.5	4.1	0.448	0.161	7.64	3.56	1.580	0.005	4.44
5. J. J.	29	H.C.V.D., ? R.H.D.	3.58	0.73	52	11.1	85.2	1.9	0.484	0.019	7.20	1.59	0.906	0.015	4.54
6. N. S.	26	Auricular septal defect	4.32	0.68	.....	14.0	91.2	2.1	1.085	0.300	5.50	1.80	.....	.....	3.95
7. E. H.	43	H.C.V.D.	2.33	0.73	90	11.9	86.6	1.1	0.339	0.034	5.87	2.51	0.985	0.030	3.96
8. F. S.	53	Syphilitic heart disease with aortic insufficiency	4.10	0.70	79	13.8	92.5	0.7	0.392	0.078	6.48	1.90	1.430	0.033	3.24
9. C. G.	32	Ventricular septal defect	4.25	0.72	.....	13.2	91.0	4.5	0.583	0.110	5.50	2.35	1.555	0.015	5.25
10. T. W.	42	Emphysema, cor pulmonale	4.18	0.58	.....	8.6	90.4	1.3	1.370	0.190	11.08	0.31	0.870	0.013	.....
11. B. C.	11	Patent ductus arteriosus	4.46	0.77	.....	11.6	90.2	3.0	0.683	0.105	7.18	1.90	0.950	0.004	.....
12. E. T.	66	H.C.V.D.	3.75	0.75	77	10.1	93.2	1.0	0.245	0.141	8.30	3.40	1.470	0.003	3.54
13. L. I.	69	H.C.V.D.	2.85	0.65	.....	12.0	74.0	2.0	0.503	0.121	8.53	2.33	1.586	0.012	3.80
14. O. B.	36	Pulmonary emphysema, cor pulmonale	4.85	0.78	.....	11.2	104.2	3.0	0.482	0.116	4.70	0.26	1.125	0.017	3.66
15. C. I.	27	R.H.D., anemia	3.80	.....	.....	6.8	95.3	1.0	0.338	0.047	7.12	1.08	.....	.....	4.80
		Range	2.15 to 5.99	0.57 to 0.82	52 to 113	6.8 to 14.9	74.0 to 104.2	0.7 to 5.6	0.245 to 1.370	0.019 to 0.300	4.44 to 11.8	0.31 to 3.56	0.870 to 1.586	0.0 to 0.033	3.24 to 5.25
		Mean	3.789	0.715	86.5	11.327	90.473	2.540	0.578	0.110	7.010	1.75	1.280	0.0147	4.100

TABLE I (*Continued*)

Extractions			Myocardial Usage (per 100 gm./min.)							Oxygen Extraction Ratio (%)							
Δ Amino Acids	Arterial Ketones (mg./100 cc.)	Δ Ketones	Oxygen (cc.)	Glucose (mg.)	Pyruvate (mg.)	Lactate (mg.)	Fatty Acids (mEq.)	Amino Acids (mg. N)	Ketones (mg.)	Glucose	Pyruvate	Lactate	Fatty Acids	Amino Acids	Ketones	Total Carbohydrates	Total Non-carbohydrates
.....	1.35	0.86	.....	.....	.....	.....	.....	.....	.....	14.7	0.50	2.2	83.8	.....	8.6	17.4	.....
0.08	2.04	0.57	9.68	1.58	0.00	1.43	0.039	0.070	0.50	12.3	0.00	11.1	228.0	3.40	5.3	23.4	236.7
0.43	0.94	0.22	8.35	4.17	0.00	2.00	0.004	0.374	0.19	37.5	0.00	18.0	29.7	21.0	2.3	55.5	53.0
0.02	4.31	1.45	9.59	6.54	0.39	0.71	0.016	0.022	1.58	51.1	0.26	5.5	97.1	1.1	16.8	56.9	115.0
0.11	2.66	0.90	.....	.....	.....	.....	.....	.....	.....	40.8	0.27	5.8	91.6	4.6	8.2	46.9	104.4
0	3.64	1.27	9.40	2.85	0.17	0.95	0.019	0	1.21	22.7	1.13	7.6	115.3	0	13.1	31.4	128.4
0.10	0.81	0.04	.....	.....	.....	.....	.....	.....	.....	7.3	0.12	11.8	122.6	5.0	0.4	19.2	128.0
0.07	0.63	0.31	.....	.....	.....	.....	.....	.....	.....	28.6	0.09	24.00	36.2	2.6	2.5	57.2	41.3
0	1.07	0.36	.....	.....	.....	.....	.....	.....	.....	24.0	0.78	8.1	0	0	3.6	32.9	3.6
.....	0.65	0.18	.....	.....	.....	.....	.....	.....	.....	3.1	1.23	17.0	255.0	.....	1.9	21.3	.....
0	2.75	1.06	7.90	0.53	0.01	0.44	0.099	0	0.70	5.0	0.04	4.2	71.3	0	9.0	9.2	80.5
0.0 to 0.43	0.63 to 4.31	0.04 to 1.45	7.90 to 9.68	0.53 to 6.54	0.0 to 0.39	0.44 to 2.00	0.004 to 0.099	0.0 to 0.374	0.19 to 1.58	3.1 to 51.1	0.0 to 1.23	2.2 to 24.0	0.0 to 255.0	0.0 to 21.0	0.4 to 16.8	9.2 to 57.2	3.6 to 236.7
0.101	1.89	0.656	8.98	3.134	0.114	1.106	0.0354	0.0932	0.836	22.46	0.4018	10.48	102.8	4.81	6.52	33.7	98.9

TABLE II (*Continued*)

Extractions			Myocardial Usage (per 100 gm./min.)							Oxygen Extraction Ratio (%)							
Δ Amino Acids	Arterial Ketones (mg./100 cc.)	Δ Ketones	Oxygen (cc.)	Glucose (mg.)	Pyruvate (mg.)	Lactate (mg.)	Fatty Acids (mEq.)	Amino Acids (mg. N)	Ketones (mg.)	Glucose	Pyruvate	Lactate	Fatty Acids	Amino Acids	Ketones	Total Carbohydrates	Total Non-carbohydrates
0.02	1.38	0.311	8.9	6.33	0.06	0.88	0.230	0.023	0.35	53.6	0.43	6.9	144.3	1.2	4.01	60.9	149.5
0.06	0.87	0.092	8.9	3.34	0.05	1.49	0	0.043	0.07	28.0	0.36	11.9	0	2.2	0.74	40.3	2.9
0.10	.....	.....	11.4	2.35	0.12	0.58	0.017	0.112	.....	15.4	0.66	3.8	83.8	4.6	.....	19.9	.....
0	0.85	0.040	14.6	4.02	0.16	3.49	0.005	0	0.04	20.6	0.69	17.9	19.1	0	0.27	39.2	19.4
0.11	0.86	0	5.8	0.99	0.01	0.83	0.008	0.057	0	12.8	0	10.7	77.1	4.6	0	23.5	81.7
0.32	1.81	0.56	.....	.....	.....	.....	.....	.....	.....	11.4	1.37	9.7	.....	10.6	4.08	22.5	.....
0	3.79	0.69	10.7	0.99	0.03	2.28	0.027	0	0.62	6.9	0.18	15.8	144.0	0	5.92	22.9	149.9
0.03	3.12	0.95	10.7	0.56	0.06	1.50	0.026	0.024	0.75	3.8	0.36	10.3	136.3	1.0	7.02	14.5	144.3
0.20	1.68	0.36	.....	.....	.....	.....	.....	.....	.....	25.6	0.53	13.4	64.8	7.1	2.78	39.5	74.7
.....	1.92	0.66	.....	.....	.....	.....	.....	.....	.....	11.3	1.42	2.7	86.2	.....	7.83	15.4	.....
.....	2.02	0.61	.....	.....	.....	.....	.....	.....	.....	19.4	0.58	12.3	19.7	.....	5.36	32.3	.....
0.12	1.92	0.23	7.8	0.77	0.11	2.61	0.002	0.093	0.18	7.4	0.89	25.2	16.9	5.6	2.32	33.5	24.8
0.05	1.67	0.38	.....	.....	.....	.....	.....	.....	.....	12.5	0.65	14.6	99.8	1.9	3.23	27.7	104.9
0.05	1.48	0.67	.....	.....	.....	.....	.....	.....	.....	20.1	0.66	1.7	86.5	2.1	6.10	22.5	94.7
.....	2.28	0.71	.....	.....	.....	.....	.....	.....	.....	11.0	0.44	11.9	.....	.....	10.65	23.3	.....
0.0 to 0.32	0.86 to 3.79	0.0 to 0.95	5.8 to 14.6	0.56 to 6.33	0.01 to 0.16	0.58 to 3.49	0.0 to 0.230	0.0 to 0.112	0.0 to 0.75	3.8 to 53.6	0.0 to 1.37	1.7 to 25.2	0.0 to 144.3	0.0 to 10.6	0.0 to 10.65	14.5 to 60.9	2.9 to 149.9
0.088	1.83	0.481	9.85	2.41	0.075	1.708	0.039	0.044	0.335	17.32	0.615	11.25	75.2	3.40	4.64	29.2	83.0

H.C.V.D. = hypertensive cardiovascular disease
R.H.D. = rheumatic heart disease

TABLE III

Patients	Age (yr.)	Diagnosis	Cardiac Index (L./M²/m.)	R.Q. of Heart	Coronary Flow (cc./100 gm./min.)	Arterial Levels and Myocardial: Δ Oxygen (vol. %)	Arterial Glucose (mg./100 cc.)	Δ Glucose	Arterial Pyruvate (mg./100 cc.)	Δ Pyruvate	Arterial Lactate (mg./100 cc.)	Δ Lactate	Arterial Fatty Acids (mEq./100 cc.)	Δ Fatty Acids	Arterial Amino Acids (mg. N/100 cc.)	Δ Amino Acids
1. J. W.	74	Senile heart disease	1.09	.....	47.0	10.0	84.1	0.8	0.506	0.072	13.00	4.20	0.873	0.021	3.53	0.23
2. L. H.	57	H.C.V.D.	1.77	1.09	.....	9.1	88.0	5.8	0.416	0.070	6.82	0.40	0.985	0.020	3.25	0.05
3. J. R.	47	H.C.V.D.	2.77	0.85	72.0	8.6	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
4. A. C.	47	H.C.V.D.	2.05	0.47	76.0	14.0	102.2	0.7	0.463	0.137	7.10	1.72	0.950	0.055	3.00	0.18
5. B. M.	67	H.C.V.D.	1.22	0.60	80.0	12.4	123.7	2.1	0.766	0.142	10.60	0.50	1.025	0.045	4.18	0.10
6. A. A.	34	Mitral stenosis and insufficiency	3.23	0.74	.....	10.3	90.1	3.5	0.561	0.140	7.82	0.96	1.026	0.006	.....	.....
7. S. M.	41	H.C.V.D.	3.10	0.97	90.5	14.2	101.2	9.1	0.421	0.070	8.23	2.48	1.285	0.020	4.26	0
8. W. G.	..	Nephrotic stage of glomerulonephritis	2.75	0.60	65.0	9.5	97.2	2.0	0.262	0.034	4.91	1.67	1.960	0.010	2.46	0.05
9. J. M.	42	A.S.H.D.	1.68	0.89	.....	10.6	91.7	2.6	0.324	0.052	8.67	0	1.065	0.080	4.55	0.35
10. R. H.	54	Rheumatic heart disease	1.40	0.71	96.0	14.8	87.7	4.7	0.583	0.055	7.08	2.28	1.723	0.096	2.39	0.23
11. L. S.	31	Polycystic disease, hypertension	2.32	0.81	.....	12.4	91.4	4.4	0.590	0.155	6.00	1.50	1.185	0.032	3.87	0.03
12. C. F.	40	H.C.V.D., A.S.H.D.	2.67	.....	79.0	8.1	106.2	2.2	0.641	0.148	6.47	0.31	0.852	0.014	4.65	0.20
13. J. W.	67	H.C.V.D.	2.15	0.71	.....	8.0	90.3	0.5	0.537	0.064	9.43	0.30	0.912	0.005	3.02	0.02
14. H. J.	29	Etiology unknown	2.05	0.72	.....	11.65	84.5	0.0	0.876	0.081	8.76	1.15	0.935	0.040	3.75	0.20
15. M. M.	58	Etiology unknown	2.96	0.74	.....	11.8	94.4	0.9	0.359	0.009	6.25	1.79	1.873	0.031	3.05	0.06
16. A. W.	47	H.C.V.D.	2.62	0.93	.....	9.4	120.1	0.9	0.463	0.113	7.56	1.08	0.975	0.000	4.98	0.12
17. V. T.	38	R.H.D.	2.15	0.78	92.0	13.9	96.6	9.1	0.639	0.138	8.55	2.50	0.795	0.000	4.15	0.00
18. D. B.	25	H.C.V.D.	2.16	0.79	64.0	12.21	.....	.....	.....	.....	.....	.....	1.440	0.000	4.36	0.32
19. E. T.	58	Auricular septal defect	2.45	0.87	54.0	10.31	90.2	7.9	0.421	0.114	7.09	3.00	0.765	0.006	4.65	0.20
20. L. W.	31	R.H.D.	2.05	0.69	.....	13.8	94.4	1.2	0.405	0.067	8.09	0.39	1.235	0.025	4.44	0.09
		Range	1.09 to 3.23	0.47 to 1.09	47.0 to 96.0	8.0 to 14.8	84.1 to 123.7	0.0 to 9.1	0.262 to 0.876	0.009 to 0.155	4.91 to 13.09	6.0 to 4.2	0.765 to 1.873	0.0 to 0.096	2.39 to 4.98	0.0 to 0.35
		Mean	2.23	0.775	74.1	11.25	96.3	2.73	0.513	0.092	7.91	1.45	1.150	0.026	3.80	0.135

H.C.V.D. = hypertensive cardiovascular disease
A.S.H.D. = arteriosclerotic heart disease
R.H.D. = rheumatic heart disease

genital heart disease, one; etiology unknown, two. The relatively low incidence of arteriosclerotic heart disease was due to the fact that the procedure was not performed in any subject who conceivably could have had a recent myocardial infarction. One possible deviation from ideal experimental conditions was that most of the patients in congestive failure had recently been taking digitalis in some form. The drug was discontinued for a few days prior to catheterization when possible. However, as another study from this laboratory has shown, usage of digitalis is not a serious objection since the administration of full digitalizing doses produces only minimal changes in myocardial metabolism under conditions identical with those used in the present investigation.[12] All patients in group III were symptomatic at the time studied, and had physical findings of failure of the left side of the heart. All but one had heart disease which primarily had affected the left ventricle. This patient (E. F.) had an auricular septal defect but in addition there was physical, roentgenologic and electrocardiographic evidence of left ventricular enlargement. Subjects with high normal or with increased cardiac output were excluded in order to prevent possible dilution of the data by other metabolic abnormalities, such as thiamin deficiency. Data on five patients whose cardiac indices were in the low normal range were included in the series, since all had severe heart failure and there was no evidence of any co-existing metabolic defect.

Excluded from the experimental group were several subjects who, despite a history of recent congestive failure and a low cardiac output, appeared to be well compensated at the time of the study. A few patients originally in groups I and II were eliminated from the series when follow-up studies altered the original diagnosis or when, in subjects belonging to group II, frank congestive failure developed soon after the study.

Procedure. All patients were studied in the post-absorptive state. The procedure was thoroughly explained and those subjects who seemed particularly apprehensive were mildly sedated with small doses of meperidine or pentobarbital. The majority received no premedication.

Cardiac catheterization was performed in the usual manner. If diagnostic studies were to be done, these were completed first. It was possible to enter the coronary sinus in about 50 per cent of the patients.

TABLE III (*Continued*)

Extractions		Myocardial Usage (per 100 gm/min)							Oxygen Extraction Ratio (%)							
Arterial Ketones (mg./100 cc.)	Δ Ketones	Oxygen (cc.)	Glucose (mg.)	Pyruvate (mg.)	Lactate (mg.)	Fatty Acids (mEq.)	Amino Acids (mg. N)	Ketones (mg.)	Glucose	Pyruvate	Lactate	Fatty Acids	Amino Acids	Ketones	Total Carbohydrates	Total Non-carbohydrates
4.82	0.32	4.71	0.38	0.034	1.98	0.010	0.108	0.15	6.0	0.46	31.5	119.7	10.8	3.3	38.0	133.8
.....	.....	.....	.....	.....	.....	.....	.....	.....	47.6	0.49	3.2	124.7	2.6	.....	51.3	.....
.....	.....	6.20	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
3.78	0.68	10.6	0.53	0.104	1.31	0.042	0.137	0.52	3.7	0.63	9.2	223.2	6.0	5.0	13.6	234.2
7.11	1.82	9.9	1.68	0.114	0.40	0.036	0.080	1.46	12.7	0.73	3.0	207.5	3.8	15.0	16.5	226.3
5.43	1.85	.....	.....	.....	.....	.....	.....	.....	26.2	0.87	7.0	33.1	.....	18.3	34.1	.....
3.94	1.14	12.8	8.23	0.063	2.24	0.018	0	1.03	48.0	0.31	13.1	80.0	0	8.2	61.4	88.2
3.76	1.34	6.1	1.30	0.022	1.08	0.006	0.036	0.87	15.9	0.23	13.2	60.2	2.7	14.4	29.3	77.3
1.42	0.16	.....	.....	.....	.....	.....	.....	.....	18.4	0.31	0.00	430.0	15.4	1.54	18.7	447.0
2.49	0.93	14.2	4.51	0.053	2.19	0.092	0.221	0.89	23.9	0.24	11.6	370.0	7.3	6.4	33.8	383.7
2.34	0.96	.....	.....	.....	.....	.....	.....	.....	26.6	0.83	9.1	147.6	1.1	7.9	36.5	156.7
1.18	0.21	6.4	1.74	0.117	0.25	0.011	0.158	0.17	20.4	1.17	2.9	98.8	11.6	2.6	24.4	113.0
3.96	0.56	.....	.....	.....	.....	.....	.....	.....	4.7	0.51	2.8	35.6	1.0	7.1	8.0	43.7
7.20	1.94	.....	.....	.....	.....	.....	.....	.....	0.0	0.45	7.4	195.7	8.0	17.0	7.8	220.7
3.43	1.59	.....	.....	.....	.....	.....	.....	.....	5.7	0.05	11.4	149.7	2.4	13.7	17.1	165.8
.....	.....	.....	.....	.....	.....	.....	.....	.....	7.2	0.77	8.6	0.00	6.0	.....	16.6	.....
5.22	1.46	12.8	8.37	0.127	2.30	0	0	1.34	49.1	0.63	13.5	0	0	10.7	63.2	10.7
.....	.....	7.8	.....	.....	.....	0	0.205	.....	.....	.....	.....	0	12.3	.....	.....	.....
0.884	0.17	5.6	4.27	0.060	1.62	0.003	0.109	0.09	57.5	0.71	21.8	33.2	9.1	1.7	80.0	44.0
0.84	0.42	.....	.....	.....	.....	.....	.....	.....	6.50	0.31	2.1	103.2	3.1	3.1	8.9	109.4
0.84	0.17	4.7	0.38	0.022	0.25	0.003	0.0	0.09	0.0	0.05	0.0	0.0	0.0	1.5	7.8	10.7
to	to	to	to	to	to	to	to	to	to	to	to	to	to	to	to	to
7.20	1.94	14.2	8.37	0.127	2.24	0.092	0.221	1.46	57.50	1.17	31.5	370.0	15.4	18.3	80.0	447.0
3.61	0.971	8.83	3.44	0.077	1.48	0.0218	0.105	0.724	21.12	0.538	9.52	126.9	5.72	8.50	31.0	163.6

Coronary flow was measured in twenty-four of the forty-six patients, using the nitrous oxide desaturation method.[6,7] Cardiac output was estimated by the direct Fick principle, the mixed venous sample being obtained from the most distal chamber entered. Expired air was collected in a Douglas bag or Tissot spirometer, and oxygen consumption determined by analysis of an aliquot of the sample, using the method of Scholander to determine the oxygen and CO_2 content of expired air.[13]

Simultaneous blood samples were collected from the coronary sinus and right femoral artery for determination of the blood concentration of oxygen, carbon dioxide, glucose, pyruvate, lactate, fatty acids, amino acids and ketones. In most cases duplicate samples were obtained and the results were averaged.

Oxygen and carbon dioxide content was determined by the manometric method of Van Slyke and Neill.[14] Blood glucose was measured by the method of Hagedorn and Jensen, using Somogyi's method to prepare the filtrates.[15,16] Pyruvate was determined according to the method of Friedemann and Haugen, using a trichloracetic acid filtrate.[17] Lactate was measured by the method of Barker and Summerson.[18] For the determination of fatty acids the method of Man and Gildea was used;[19] this is essentially a modification of the procedure of Stoddard and Drury's volumetric analysis.[20] Amino acids were estimated according to the method of Albanese and Irby.[21] Ketone content was determined by a modification of the micromethod of Greenberg and Lester.[22]

Calculations. Cardiac index was calculated by dividing the cardiac output, calculated from the Fick equation, by the body surface area as estimated from the height and weight. To determine the respiratory quotient (RQ) of the heart, the coronary arteriovenous CO_2 difference (carbon dioxide produced) was divided by the coronary arteriovenous O_2 difference (oxygen consumed). The myocardial extraction of the various metabolites was calculated as the coronary sinus content per 100 cc. subtracted from the arterial content per 100 cc. In the discussion, myocardial extraction and coronary arteriovenous difference are used interchangeably. The myocardial usage was calculated by multiplying the myocardial extraction by the coronary flow. Since the coronary flow by the method used is expressed as cubic centimeters per 100 gm. of heart muscle per minute, the myocardial usage denotes the weight or volume of the metabolite extracted from coronary blood by 100 gm. of myocardium during the period of one minute. The oxygen extraction ratio was obtained as the product of the myocardial extraction times the oxygen equivalent of the metabolite in question, divided by the simul-

taneous myocardial oxygen extraction.* The oxygen extraction ratio of a particular foodstuff represents the percentage of the total myocardial oxygen extraction which could be accounted for by the oxygen that would be required for complete catabolism of the foodstuff to CO_2 and water. Since a foodstuff may be temporarily stored by the heart or undergo conversion to another substance within the metabolic pool, the sum of the oxygen extraction ratios of all foodstuffs utilized at a given moment need not total 100 per cent.

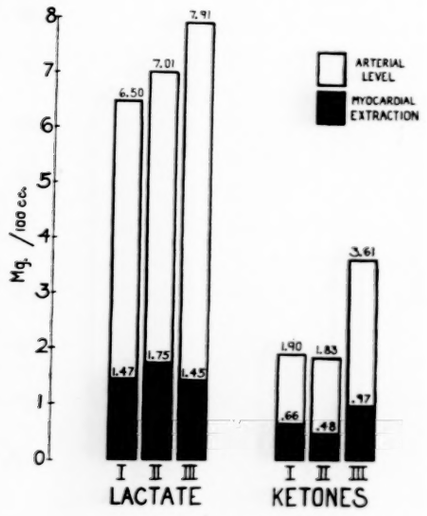


FIG. 1. The arterial concentrations of both lactate and ketones were significantly elevated in patients with congestive heart failure (group III). Myocardial ketone extraction was increased in proportion to the arterial level. In contrast the extraction of lactate was not elevated.

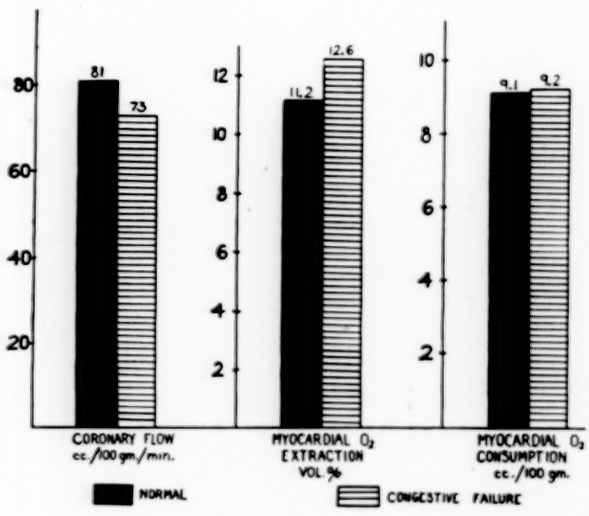


FIG. 2. Myocardial oxygen consumption (O_2 extraction × coronary flow). In twenty-two patients with congestive failure the mean coronary flow was slightly lower than the average found in sixteen normal subjects. However, the coronary arteriovenous oxygen difference in the decompensated patients was sufficiently increased so that the oxygen consumed by equal weights of heart muscle was the same in both groups.

The results obtained were tabulated by group, together with the range and mean for each determination. All the data were subjected to statistical analysis, and each group compared to the other two. Differences were not considered significant unless the probability was less than .05.[23,24]

In the following discussion the values given refer to the mean for the group, unless otherwise indicated. The normal subjects are referred to as group I, the patients with heart disease but without failure as group II, and the congestive failure patients as group III. Unless the results in group II deserve special mention, the discussion will be concerned chiefly with comparisons between groups I and III.

RESULTS

The individual observations with the mean and range for each group are shown in Tables I, II and III which correspond to groups I, II and III, respectively. Statistical comparisons between groups are summarized in Table IV, and attention is called to significant differences by an asterisk (*). To aid in comparisons, mean values of the more interesting findings are summarized in Figures 1 through 4.

Cardiac Index and Respiratory Quotient. The cardiac indices in the control groups (Tables I and II) were practically identical, averaging 3.80 and 3.81 L./sq. M./min. In the patients with congestive failure the mean cardiac index was 2.23 L./sq. M./min., which is significantly lower than in either control series. ($p < .01$, Table IV.) Although the cardiac output is usually diminished in heart failure, in the present series the low value was to be expected since it was one of the criteria for selection of subjects for group III.[25]

The mean respiratory quotients were 0.75, 0.72 and 0.78 for groups I, II and III, respectively. Because of the wide scatter within each group, however, the differences were not significant. (Table IV.) The average for all forty-six subjects was 0.75, indicating that the energy requirements of the heart in the postabsorptive state are met chiefly by non-carbohydrate foodstuffs. The total carbohydrate oxygen extraction ratios in all three groups averaged about 30 per cent,

* The oxygen equivalent values used in this calculation were: glucose, 0.75; pyruvate, 0.64; lactate, 0.75; amino acids, 4.68; fatty acids, 570; ketones, 1.02.

providing additional evidence for the predominant usage of non-carbohydrate material by the heart under basal conditions.

Coronary Flow, Myocardial Oxygen Extraction and Oxygen Consumption. The coronary flow in the five normal subjects in whom it was measured averaged 89 cc./min./100 gm. In group II the average for eight determinations was 86 cc./min./100 gm. In the congestive failure group the flow was measured in eleven subjects, the average being lower, 74 cc./min./100 gm. The probability value of group III versus group I was $> .20$, and for group III versus group II it was $> .10$. (Table IV.) Although the differences were therefore not significant by the criteria used, the tendency for a diminished coronary flow in the congestive failure patients is of possible importance in view of the correspondingly increased myocardial oxygen extractions.

In the normal subjects (Table I) the coronary arteriovenous oxygen difference was 10.4 volumes per cent, compared with 11.2 volumes per cent in the failure group. (Table III.) Here again the differences are not significant ($p > .20$, Table IV.) However, the slightly higher oxygen extraction in group III was sufficient to compensate for the diminished flow; as a result, the oxygen usage per 100 gm. of myocardium was the same in the congestive failure group as in the normals. (8.8 cc./min./100 gm., Table III; 9.0 cc./min./100 gm., Table I; $p > .90$, Table IV.) This finding confirms results previously reported.[3,26]

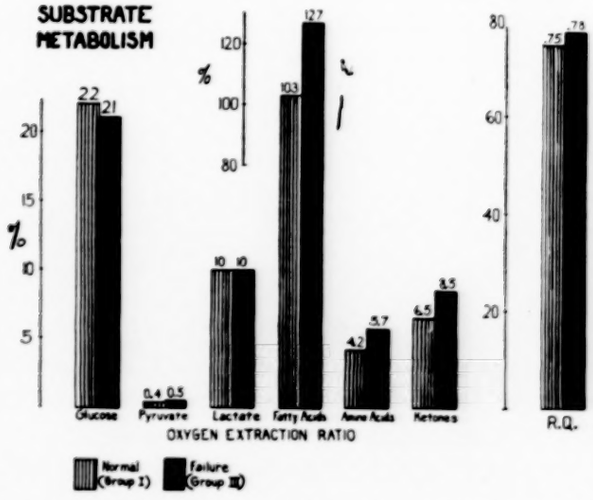


FIG. 3. Relative contribution of the individual foodstuffs to the oxidative metabolism of the normal and failing heart. It may be seen that the differences between the two groups are minimal. The respiratory quotients are the same in the two groups.

Glucose, Pyruvate, Lactate Metabolism. The myocardial extraction and usage of glucose was not significantly altered by the presence of compensated heart disease or congestive heart failure. The extraction of glucose in the three groups was 3.08, 2.54 and 2.73 mg./100 cc. (Tables I to III.) The mean oxygen extraction ratios for glucose were similar, with values of 22, 17 and 21 per cent.

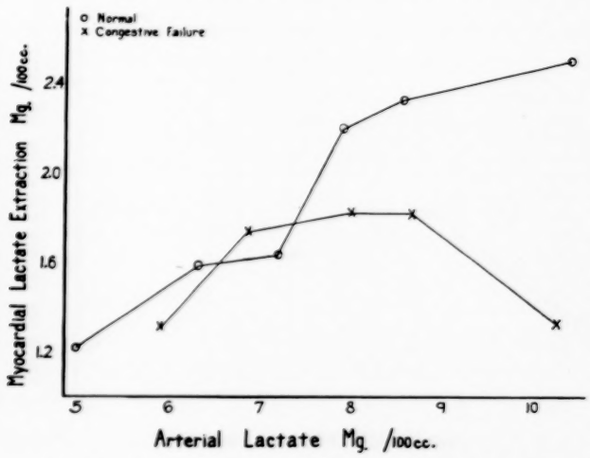


FIG. 4. Myocardial lactate extraction in normal subjects is proportional to the arterial lactate concentration. In patients with congestive failure, however, higher arterial levels are accompanied by a relative decrease in myocardial extraction. This finding suggests that lactate production in heart muscle is increased, possibly as a result of glycolysis. Points shown on the graph are mean values of individual determinations grouped according to arterial concentration.

There was no significant difference in the extraction or utilization of pyruvate. The normal myocardium extracted 0.06 mg./100 cc., compared to 0.11 mg./100 cc. in group II, and 0.09 mg./100 cc. in the failure group. The relatively small contribution to total aerobic energy production of the heart supplied by the oxidation of pyruvate is indicated by the low oxygen extraction ratios, which were close to 0.5 per cent in all three groups.

From the results shown in Figure 1 it can be seen that the average arterial lactate concentration was significantly higher in the patients with congestive failure than in the normal subjects ($p < .05$, Table IV), the means being 7.91 mg./100 cc. in group III and 6.50 mg./100 cc. in group I. The myocardial lactate extraction and usage, however, showed no significant differ-

TABLE IV

Comparison	Cardiac Index	R.Q. of Heart	Coronary Flow	Arterial Levels and Myocardial Δ Oxygen	Arterial Glucose (mg./100 cc.)	Δ Glucose	Arterial Pyruvate (mg./100 cc.)	Δ Pyruvate	Arterial Lactate (mg./100 cc.)	Δ Lactate	Arterial Fatty Acids (mEq./100 cc.)	Δ Fatty Acids	Arterial Amino Acids (mg. N/100 cc.)	Δ Amino Acids
Group I versus group II:														
x	−.0143	−.0359	−2.50	.918	−2.80	.5418	.05120	.04707	.5055	.2782	.1324	.003765	.0597	.01292
Sx	.3879	.04469	10.931	.7613	3.632	.71155	.10489	.027745	.6177	.4121	.3533	.0048895	.24172	.051807
p	>.90	>.40	>.70	>.20	>.40	>.40	>.60	>.10	>.40	>.50	>.70	>.50	>.70	>.70
Group II versus group III:														
x	1.5567	−.0606	12.36	.081	5.86	.1989	.06553	.107789	.9028	.29278	.1303	.01194	−.2930	.04667
Sx	.2707	.04294	8.3827	.7586	3.281	.96938	.08133	.020167	.6232	.3772	.1176	.007842	.2586	.038105
p	<.01*	>.10	>.10	>.90	>.05	>.80	>.40	>.30	>.10	>.40	>.20	>.10	>.20	>.20
Group I versus group III:														
x	1.5710	.0247	−14.86	.837	3.06	.3429	.01533	.02928	1.4083	.0146	.0020	.008175	.2333	.00375
Sx	.2721	.055758	8.441	.704	4.3058	1.1607	.06639	.020869	.64135	.4201	.1245	.0064737	.29131	.05014
p	<.01*	>.60	>.20	>.20	>.50	>.70	>.80	>.10	<.05*	>.90	>.90	>.20	>.40	>.50

x = difference between means
Sx = standard error of the mean
p = probability
* = significant difference

ence. Since lactic acid is the end product of glycolysis, a process which occurs in skeletal muscle during hypoxia or when aerobic energy production is insufficient to meet metabolic demands, the increased arterial concentration in the present series of patients with heart failure can be interpreted as an indication of insufficient tissue oxygenation.[27]

Amino Acids, Fatty Acids and Ketones. In the normal controls the arterial concentration of amino acid nitrogen was 4.04 mg. N/100 cc. and the myocardial extraction, 0.10 mg. N/100 cc. (Table I.) Oxidation of this amount of amino acids could account for 4.2 per cent of the simultaneous oxygen extraction. No significant differences were noted in either group II or group III.

Although no significant differences were noted in the extraction or usage of fatty acids, their importance to the total economy of the heart is well illustrated by their large contribution to energy production in all three groups studied. In normal subjects the myocardium extracted an average of 0.018 mEq./100 cc. fatty acids, compared to 0.015 mEq./100 cc. in group II, and 0.027 mEq./100 cc. in group III. (Group II versus group III, $p > .10$, Table IV.) Both in subjects with congestive failure and in normal persons the mean fatty acid oxygen extraction ratio was more than 100 per cent. Since the studies were performed with the subjects in the basal state, extraction of fatty acids in excess of immediate energy requirements could be explained by temporary storage in the myocardium for use during periods of increased energy requirements.[9] The observation by Visscher that the total lipid content of the heart decreased during cardiac work might be cited as additional evidence for this possibility.[28]

In Figure 1 it can be seen that the arterial ketone concentration was significantly higher in the patients with congestive failure (3.61 mg./100 cc.) than in either the normai subjects (1.90 mg./100 cc., $p < .01$) or in patients with compensated heart disease (1.83 mg./100 cc., $p < .02$). The myocardial ketone extraction and oxygen extraction ratio in the failure group was correspondingly increased, reflecting the general rule that the myocardial extraction of a particular substrate is dependent upon its arterial concentration.[8,9] The increased ketonemia in patients with congestive failure probably does not reflect any metabolic defect due specifically to the impaired state of the circulation. Among the possible explanations the most likely would appear to be simple "starvation" ketosis, since the anorexia accompanying severe congestive failure may preclude adequate food intake. In the decompensated cardiac patients reported in this study, the severity of symptoms

TABLE IV (*Continued*)

Extractions		Myocardial Usage (per 100 gm./min.)							Oxygen Extraction Ratio (%)							
Arterial Ketones (mg./100 cc.)	Δ Ketones	Oxygen (cc.)	Glucose (mg.)	Pyruvate (mg.)	Lactate (mg.)	Fatty Acids (mEq.)	Amino Acids (mg. N)	Ketones (mg.)	Glucose	Pyruvate	Lactate	Fatty Acids	Amino Acids	Ketones	Total Carbohydrates	Total Noncarbohydrates
.0633	−.1749	.866	.7153	.039	.6015	.0040	.0492	.501	5.14	.2129	.7733	27.51	.7739	1.8835	4.5612	13.98
.4233	.15896	1.2325	.3878	.0629	.50596	.03765	.05796	.26139	5.4754	.16432	2.5253	26.319	2.1698	166.58	5.807	29.579
>.80	>.20	>.40	>.05	>.50	>.20	>.90	>.40	>.05	>.30	>.20	>.70	>.30	>.70	>.20	>.40	>.60
1.7804	.4904	1.0155	1.0269	.00211	−.2219	−.01758	.0614	.3894	3.80	.0758	−1.7305	51.69	2.3173	3.8664	1.8850	78.62
.5806	.1916	1.4337	1.2944	.02170	.4350	.02642	.030615	.23472	5.495	.1158	2.4576	35.03	1.5385	1.7367	6.149	44.013
<.01*	<.02*	>.40	>.40	>.90	>.60	>.50	>.05	>.10	>.40	>.50	>.40	>.10	>.10	<.05*	>.70	>.05
1.7171	.3155	.1495	.3116	.0369	.3796	.0136	.0122	.112	1.34	.1371	.9572	24.18	1.5434	1.9829	2.6764	64.64
.69159	.2265	1.5502	1.6056	.05766	.4079	.017355	.06015	.29627	6.6212	.13512	2.8184	40.24	2.1797	2.1401	7.589	44.7997
<.02*	>.10	>.90	>.80	>.50	>.30	>.40	>.80	>.70	>.80	>.30	>.70	>.50	>.40	>.30	>.70	>.10

may be judged from the fact that admission to the hospital was required.

DISCUSSION

Oxygen Consumption. The myocardial oxygen consumption of the normal subjects in this series, based on the determination of coronary flow in five persons, is 8.8 cc./100 gm./min. In the congestive failure group the oxygen consumption is 9.0 cc./100 gm./min., calculated from coronary flow measurements in eleven subjects. Further evidence for the fact that there is no significant difference between the two groups can be obtained by combining the results of the present study with findings reported in previous publications from this laboratory.[4,26] In this manner data can be presented on a total of sixteen normal subjects and twenty-two with left ventricular failure in whom simultaneous determinations of the coronary flow and myocardial oxygen extraction were made. These results are shown in Figure 2.

Again it can be seen that the patients with congestive failure have a lower average coronary flow (73 cc./100 gm./min. versus 81 cc./100 gm./min.) but a higher myocardial oxygen extraction (12.6 vol. per cent versus 11.2 vol. per cent) than do the normal subjects. Calculations of the myocardial oxygen consumption from these data give values of 9.1 cc./100 gm./min. in the normal subjects and 9.2 cc./100 gm./min. in the patients with left ventricular failure. It is therefore concluded that the oxygen consumed by equal weights of heart muscle is the same in both groups.

Substrate Utilization. From the data presented it appears that the over-all pattern of foodstuff utilization by the myocardium is not altered in the presence of congestive heart failure. No significant differences in myocardial usage of any of the basic foodstuffs can be demonstrated in the three groups studied. Although the increase in myocardial extraction of ketones noted previously is statistically significant, the myocardial ketone usage is not significantly elevated since the increase in ketone extraction is small. (Table IV.) Rather than indicating the presence of a metabolic abnormality, the ability of the failing heart to increase the extraction of ketones in proportion to the elevated arterial ketone level demonstrates the similarity of the metabolic response to that of normal heart muscle.

The similarity of the pattern of foodstuff utilization is further evidenced by the respiratory quotients which show similar mean values in all three groups, despite marked variations between persons within each group.

Since significant elevations in the arterial level of both lactate and ketones were found in the patients with cardiac failure, it appears that the metabolic changes occurring in the tissues as a result of congestive heart failure are more pronounced than those demonstrated within the myocardium.

Energy Metabolism. In evaluating the signifi-

cance of the results of this study it is helpful to review first the essential features of normal myocardial metabolism and then to consider the possible deficiencies in energetics which could result in diminished external cardiac work. To aid in localizing any such deficiencies the total metabolic process may be conveniently divided into two phases: energy production and energy utilization.[2,29,30]

Cardiac muscle is richly supplied with oxygen and oxidative enzymes. Under physiologic conditions energy production is therefore thought to be almost entirely an aerobic process.[30,31] Substrates extracted from coronary blood are catabolized by a complex system of stepwise enzymatic reactions, the net result of which is the liberation of free energy from the substrate, the consumption of oxygen and production of CO_2 and water. Part of this energy is dissipated as heat but approximately 65 per cent is captured as phosphate bond energy, chiefly by phosphocreatine which then acts as a temporary reservoir for high energy phosphate bonds.[32,33] Utilization of the phosphate bond energy made available by substrate catabolism is thought to be mediated through adenosinetriphosphate (ATP) which supplies energy as needed for anabolic reactions and other cell work.[31] In cardiac muscle the energy supplied is utilized to initiate shortening of the contractile protein actomyosin, thereby transforming chemical energy into mechanical energy.[34,35]

Since the present investigation provides pertinent data regarding both oxygen consumption and substrate extraction, it should be possible to compare the patterns of myocardial energy production in normal subjects and patients with congestive failure. If it can be shown that energy production is quantitatively similar in both groups, then the reduction in external work of the heart characteristic of the type of cardiac failure under consideration must be due to inefficient energy utilization.

If myocardial metabolism in human subjects is predominantly an aerobic process and energy is produced by the oxidative catabolism of substrates, it should be possible to use oxygen consumption as an index of energy production. In order to make valid comparisons in this manner it must be demonstrated that: (1) the same type of fuel is consumed by normal and failing hearts, since the energy yield from equivalent volumes of oxygen varies according to the type of foodstuff catabolized; (2) no energy is derived from anaerobic mechanisms, or that the amount so derived is equal in both conditions.[36]

The first question has already been answered, since it has been shown that the pattern of foodstuff usage in congestive failure is not altered sufficiently to have any effect on total quantity of energy released by oxidative catabolism. From analysis of the respiratory quotients and the oxygen extraction ratios of the individual foodstuffs, as shown in Figure 3, it appears that both normal and failing human hearts under basal conditions derive about 30 per cent of their energy requirements from carbohydrates, 5 per cent from amino acids, 7 per cent from ketones and the remainder from fatty acids.

Although the second question is more difficult to answer, evaluation of lactate metabolism in patients with congestive failure and consideration of previous work in experimental animals should permit an estimate of the possible role of anaerobiosis as a means of energy production in heart muscle.

Anaerobic Metabolism. Since the myocardium is continuously active, sufficient oxygen and respiratory enzymes are available to permit a high rate of aerobic metabolism. Skeletal muscles, in which activity usually alternates with periods of rest, are as a rule less well endowed with oxidative enzyme systems. When such muscles become active, glycolysis takes place in addition to respiration in an effort to fulfill the energy requirements.[31] Since no immediate oxygen is required, glycolysis provides a method for producing energy during hypoxia. Following cessation of activity or restoration of oxygen supply, however, oxygen consumption proceeds at a rate in excess of immediate energy requirements until glycogen stores have been replaced and surplus lactic acid consumed. The oxygen required for this purpose is the "oxygen debt."[31,36]

The finding of a significantly increased arterial lactate concentration in patients with congestive failure (Fig. 1, Table III) suggests that tissue oxygenation is inadequate for optimal aerobic energy production. Other observers have reported similar findings. Meakins and Long, for example, found that in comparison to normal subjects the concentration of lactic acid in the blood of subjects with congestive failure rose higher for a given amount of exercise and remained elevated longer.[37] In severe cases the resting level was elevated, the amount of

elevation correlating well with the severity of the clinical condition of the patient. Weiss and Ellis, on the other hand, could find no significant elevation of lactate in resting cardiac patients but were able to document the increased rise following exercise and the delayed return of blood lactate level to normal after exercise ceased.[38] Harris, Jones and Aldred also found generally higher concentrations of lactic acid in the peripheral blood of subjects with congestive failure.[39]

In contrast to the situation in skeletal muscle, normal cardiac muscle is apparently able to increase its aerobic metabolism sufficiently to perform increased work, within physiologic limits, without resort to glycolysis. Numerous observers have reported studies in experimental animals demonstrating that the myocardium does not contract a significant oxygen debt during increased cardiac work.[40,41] However, it is likely that the apparent difference in energy producing mechanisms is quantitative rather than qualitative, since under conditions of marked hypoxia the lactate concentration of coronary sinus blood may exceed that of arterial blood, indicating the occurrence of significant glycolysis.[40] For example, if the oxygen supply of the heart-lung preparation is gradually reduced, the extraction of lactate by the myocardium decreases progressively until at oxygen saturation levels of about 24 per cent, the lactic acid in coronary venous blood exceeds that of arterial blood.[42,43] More recently, a similar process was demonstrated following embolization of the coronary circulation of the intact dog by plastic microspheres.[44]

Similar studies from this laboratory have further indicated that ischemia of the heart muscle results in alterations in myocardial extraction of pyruvate and glucose, as well as of lactate. This suggests that severe myocardial ischemia results in disturbances in certain enzyme and coenzyme systems within the muscle cell.[2] It appears significant that in myocardial failure no disturbances in myocardial pyruvate or glucose extraction are present.

From consideration of the glycolytic process in skeletal muscle, and from the behavior of lactate metabolism in the myocardium of hypoxic animals, it is inferred that if anaerobiosis occurs in cardiac muscle of human subjects with cardiac failure, it should be detected first by diminished extraction of lactate from coronary blood. As energy demands increase, or oxygen supply diminishes, lactate production should increase until the rate of production exceeds the rate of utilization, at which point the concentration in coronary venous blood should exceed that in arterial blood. Since in the present study the subjects were in nearly basal conditions and no evidence of decreased oxygen consumption was found, only minimal changes in lactate metabolism would be expected.

Review of the results shown in Figure 1 and Table III indicates that such a process may actually occur in some of the patients with congestive heart failure. It is noted in Figure 1 that despite the significantly increased arterial lactate concentration in the group as a whole, myocardial extraction was not elevated. Analysis of the individual observations demonstrates that diminished lactate extraction is evident chiefly in those subjects with the higher arterial levels. (Table III.) In contrast to the results in patients with left ventricular failure, the subjects in the control groups show no decreased lactate extraction at higher arterial levels. The curves derived from the individual data demonstrate the difference in the two groups and also show that the relative decrease in myocardial lactate extraction in subjects with heart failure was not evident at arterial levels below 7.5 mg./100 cc. (Fig. 4.)

Despite the suggestive evidence for myocardial anaerobiosis in some of the patients with congestive failure, it is unlikely that the amount of energy liberated by glycolysis is sufficient under basal conditions to alter substantially the total energy production of the heart as calculated from oxygen consumption. That anaerobic catabolism is only minimal under basal conditions is indicated by the fact that the coronary venous lactate concentration exceeded the arterial level in only one subject (J. M.). (Table III.) It is possible, however, that when activity is increased above basal levels, the failing heart may be unable to increase its aerobic energy production in proportion to the work requirements, and anaerobic catabolism occurs in an attempt to fill the deficit. The inefficiency of the glycolytic process as a means of energy production could partially explain the diminished ability of the heart in subjects with congestive failure to increase its output during exercise.

In the preceding discussion it has been demonstrated that no appreciable difference exists

between the normal and the failing human heart in either oxygen consumption or the pattern of substrate utilization. Since anaerobic catabolism is only minimal, if it occurs at all under basal conditions, it may be concluded that there is no difference in energy production in equal weights of cardiac muscle. Because of myocardial hypertrophy in patients with congestive failure, the total energy released is actually increased. The failing heart must therefore be deficient in its ability to utilize energy for effective muscular contraction even under basal conditions, since the mechanical work performed is normal or decreased. It is likely that the deficiency resides within the contractile proteins of heart muscle.

SUMMARY

The metabolism of the human heart in low output congestive failure has been investigated using coronary sinus catheterization. Results obtained from twenty patients with left ventricular failure were statistically compared with data collected from eleven normal subjects and fifteen patients with compensated heart disease.

In comparison with normal subjects, patients with congestive failure had slightly decreased mean coronary flow and slightly elevated myocardial oxygen extraction. The oxygen consumption per 100 gm. of heart muscle was normal.

The arterial concentration of both lactate and ketones was significantly increased in patients with decompensated heart disease. Despite the elevated arterial lactate concentration, extraction of lactate by the failing myocardium was not increased. Impairment of myocardial lactate utilization was further suggested by a relative decrease in myocardial lactate extraction occurring only at high arterial lactate levels. Although these changes were only minimal in resting patients, they suggest that glycolysis may occur in the failing heart when energy demands are increased.

Myocardial usage of glucose, pyruvate, fatty acids, amino acids and ketones was not altered in the presence of compensated heart disease or frank congestive failure.

Energy production per 100 gm. of heart muscle was normal in patients with congestive failure. However, total available energy was increased because of the accompanying cardiac hypertrophy. Since the mechanical work performed was normal or decreased, the failing heart would appear to be deficient in its ability to utilize energy for effective muscular contraction. It is likely that this failure of energy utilization is the result of changes in the contractile proteins of failing heart muscle.

REFERENCES

1. Bing, R. J., Vandam, L. D., Gregoir, F., Handelsman, J. C., Goodale, W. T. and Eckenhoff, J. E. Catheterization of the coronary sinus and middle cardiac vein in man. *Proc. Soc. Exper. Biol. & Med.*, 66: 239, 1947.
2. Bing, R. J. The metabolism of the heart. *Harvey Lect.* Series L. 27. New York, 1956. Academic Press, Inc.
3. Bing, R. J., Hammond, M. M., Handelsman, J. C., Powers, S. R., Spencer, F. C., Eckenhoff, J. E., Goodale, W. T., Hafkenschiel, J. H. and Kety, S. S. The measurement of coronary blood flow, oxygen consumption, and efficiency of the left ventricle in man. *Am. Heart J.*, 38: 1, 1949.
4. Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H. and Banfield, W. A. Coronary sinus catheterization for studying coronary blood flow and myocardial metabolism. *Am. J. Physiol.*, 152: 340, 1948.
5. Gregg, D. E. Coronary Circulation in Health and Disease. Philadelphia, 1950, Lea & Febiger.
6. Spencer, F. C., Merrill, D. L., Powers, S. R. and Bing, R. J. Coronary blood flow and cardiac oxygen consumption in unanesthetized dogs. *Am. J. Physiol.*, 160: 149, 1950.
7. Goodale, W. T. and Hackel, D. B. Measurement of coronary blood flow in dogs and man from rate of myocardial nitrous oxide desaturation. *Circulation Res.*, 1: 502, 1953.
8. Bing, R. J., Siegel, A. L., Vitale, A., Balboni, F., Sparks, E., Taeschler, M., Klapper, M. and Edwards, W. S. Metabolic studies on the human heart *in vivo*. I. Studies on carbohydrate metabolism of the human heart. *Am. J. Med.*, 15: 284, 1953.
9. Bing, R. J., Siegel, A. L., Ungar, I. and Gilbert, M. Metabolism of the human heart. II. Studies on fat, ketone and amino acid metabolism. *Am. J. Med.*, 16: 504, 1954.
10. Ungar, I., Gilbert, M., Siegel, A. L., Blain, J. M. and Bing, R. J. Studies on myocardial metabolism. IV. Myocardial metabolism in diabetes. *Am. J. Med.*, 18: 385, 1955.
11. Goodale, W. T., Olson, R. E. and Hackel, D. B. Myocardial glucose, lactate and pyruvate metabolism of normal and failing hearts studied by coronary venous catheterization in man. *Federation Proc.*, 9: 49, 1950.
12. Blain, J. M., Eddleman, E. E., Siegel, A. L. and Bing, R. J. Studies in myocardial metabolism. V. The effects of Lanatoside-C on the metabolism of the human heart. *J. Clin. Investigation*, 35: 314, 1956.
13. Scholander, P. F. Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. *J. Biol. Chem.*, 167: 235, 1947.
14. Van Slyke, D. D. and Neill, J. M. Determination of gases in blood and other solutions by vacuum

extraction and manometric measurement. *J. Biol. Chem.*, 61: 523, 1924.
15. Hagedorn, H. C. and Jensen, B. N. Zur Mikrobestimmung des Blutzuckers mittels Ferricyanid. *Biochem. Ztschr.*, 135: 46, 1923.
16. Somogyi, M. Method for preparation of blood filtrates for determination of sugar. *J. Biol. Chem.*, 86: 655, 1930.
17. Friedemann, T. E. and Haugen, G. E. Pyruvic acid; determination of keto acids in blood and urine. *J. Biol. Chem.*, 147: 415, 1943.
18. Barker, S. B. and Summerson, W. H. Colorimetric determination of lactic acid in biological material. *J. Biol. Chem.*, 138: 535, 1941.
19. Man, E. B. and Gildea, E. F. A modification of the Stoddard and Drury titrimetric method for the determination of the fatty acids in blood serum. *J. Biol. Chem.*, 99: 43, 1932.
20. Stoddard, J. L. and Drury, P. E. A titration method for blood fat. *J. Biol. Chem.*, 84: 741, 1929.
21. Albanese, A. A. and Irby, V. Determination of amino nitrogen of blood filtrates by copper method. *J. Lab. & Clin. Med.*, 30: 718, 1945.
22. Greenberg, L. A. and Lester, D. Micromethod for determination of acetone and ketone bodies. *J. Biol. Chem.*, 154: 177, 1944.
23. Lacey, O. L. Statistical Methods in Experimentation: an Introduction. New York, 1953. The Macmillan Co.
24. Fisher, R. A. Statistical Methods for Research Workers, 8th ed. Edinburgh, 1941. Oliver & Boyd.
25. Stead, E. A., Jr., Warren, J. V. and Brannon, E. S. Cardiac output in congestive heart failure. *Am. Heart J.*, 35: 529, 1948.
26. Bing, R. J., Maraist, F. M., Dammann, J. F., Draper, A., Jr., Heimbecker, R., Daley, R., Gerard, R. and Calazel, P. Effect of strophanthus on coronary blood flow and cardiac oxygen consumption of normal and failing human hearts. *Circulation*, 2: 513, 1950.
27. Bodansky, M. and Bodansky, O. Biochemistry of Disease, p. 147. New York, 1952. The Macmillan Co.
28. Visscher, M. B. Fat metabolism of the isolated heart. *Proc. Soc. Exper. Biol. & Med.*, 38: 323, 1938.
29. Wollenberger, A. The energy metabolism of the failing heart and the metabolic action of the cardiac glycosides. *Pharmacol. Rev.*, 1: 311, 1949.
30. Olson, R. E. and Schwartz, W. B. Myocardial metabolism in congestive heart failure. *Medicine*, 30: 21, 1951.
31. Hawk, P. B., Oser, B. L. and Summerson, W. H. Practical Physiological Chemistry, 13th ed., p. 275. New York, 1954. The Blakiston Co.
32. Ball, E. G. Energy relationships of the oxidative enzymes. *Ann. New York Acad. Sc.*, 45: 363, 1944.
33. Lipmann, F. Metabolic generation and utilization of phosphate bond energy. *Advances Enzymology*, 1: 99, 1941.
34. Szent-Gyorgyi, A. The Chemistry of Muscular Contraction. New York, 1948. New York Academic Press.
35. Wollenberg, A. Metabolic action of the cardiac glycosides. II. Effect of ouabain and digoxin on the energy-rich phosphate content of the heart. *J. Pharmacol. & Exper. Therap.*, 103: 123, 1951.
36. Best, C. H. and Taylor, N. B. The Physiological Basis of Medical Practice, 6th ed., p. 717. Baltimore, 1955. Williams & Wilkins Co.
37. Meakins, J. and Long, C. N. H. Oxygen consumption, oxygen debt and lactic acid in circulatory failure. *J. Clin. Investigation*, 4: 273, 1927.
38. Weiss, S. and Ellis, L. B. Oxygen utilization and lactic acid production in extremities during rest and exercise in subjects with normal and in those with diseased cardiovascular systems. *Arch. Int. Med.*, 55: 665, 1935.
39. Harris, I., Jones, C. W. and Aldred, C. N. Blood pH and lactic acid in different types of heart disease. *Quart. J. Med.*, 4: 407, 1935.
40. Evans, C. L. The metabolism of cardiac muscle. In: Recent Advances in Physiology, 6th ed. Philadelphia, 1939. The Blakiston Co.
41. Clark, A. J. and White, A. C. The oxygen consumption of the frog's heart. I. *J. Physiol.*, 66: 185, 1928.
42. Bogue, Y. J., Chang, I. and Gregory, R. A. Metabolism of isolated mammalian heart under partial anoxia. *Quart. J. Exper. Physiol.*, 27: 319, 1938.
43. Ruhl, A. and Thadden, S. Die Wirkung von Caffein auf den Milchsäurestoffwechsel von Herz and Lunge. *Arch. f. exper. Path. u. Pharmakol.*, 191: 438, 1939.
44. Bing, R. J., Eddleman, E. E., Edwards, W. S., Schafer, H. and Siegel, A. L. Studies in myocardial metabolism. V. Myocardial metabolism following artificial coronary occlusion and ventricular fibrillation. *Am. Heart J.*, in press.

Mechanisms of QRS Complex Prolongation in Man*

Left Ventricular Conduction Disturbances

ROBERT P. GRANT, M.D. *and* HAROLD T. DODGE, M.D.
Bethesda, Maryland

PRESENT concepts of the mechanism of the QRS complex changes that take place with ventricular conduction disturbances in man are based nearly entirely upon electrocardiographic studies made before and after interruption of one or another conduction pathway in experimental animals.[1,2] No similar studies have been possible in man. The nearest approach to this has been the recording of intracavitary and intramural QRS potentials in subjects with previously acquired conduction defects.[3–5] Such measurements indicate the general distribution of electrical positivity and negativity across the septum and across the myocardial wall from instant to instant during the QRS cycle but the measurements cannot be expressed in the form of directed electrical forces, and quantitative studies therefore are not possible. In addition, the extent to which intramural potentials play a part in writing the body surface QRS complexes of the clinical tracing is unknown, and the significance of these findings in clinical electrocardiography is unclear. Finally, the studies cannot be properly controlled because the characteristics of the potentials prior to the conduction defect are not known. While this method of study has shed light on many aspects of electrocardiography, and especially on the genesis of QRS potentials in the dog, it has not been critically helpful in explaining the varieties of QRS "patterns" seen in conduction disturbances in man.

The use of vector technics for analysis of conventional clinical body surface deflections makes possible a new approach to this problem. Since in this method the information in all body surface leads of a given patient is integrated into the form of single electrical forces, it is quite simple to make accurate quantitative comparisons of two tracings in the same patient. By comparing the electrical forces in a tracing showing normal ventricular conduction with those in a tracing showing the conduction defect, it is possible to measure and study in detail the changes in the QRS electrical field which had taken place with the conduction defect. This is the approach used in the present study and it would appear to be the first controlled study of ventricular conduction disturbances in man, the control for each case being the tracing showing normal ventricular conduction.

Two hundred and twenty-three cases were collected with tracings showing QRS prolongation of .12 second or more; in all patients there were one or more tracings showing normal conduction either before or after (or both before and after) tracings with QRS prolongation. Of these, 128 showed QRS complexes in the various leads which would be classified as left bundle branch block by conventional criteria (that is, a QRS interval of .12 second or more with a leftward QRS axis in the presence of normal sinus rhythm), and these cases are the subject of the present report. In a later paper the remaining patients, including those fulfilling classical criteria for diagnosis of right bundle branch block, will be presented.

The results of the present study indicate that (1) the classical explanation of left bundle branch block, which is based upon animal experimentation, is only partially accurate when applied to human left bundle branch block, that (2) there are other causes of QRS prolongation of the leftward type in man besides left bundle branch block, and that (3) myocardial infarction in certain cases produces a QRS prolonga-

* From the Laboratory of General Medicine and Experimental Therapeutics, National Heart Institute, National Institutes of Health, Bethesda, Maryland.

TABLE 1

Control Tracing	Normal	Left Axis Deviation	Left Ventricular Strain	Antero-lateral Infarction	Diaphrag-matic Infarction	Strictly Posterior Infarction	Strictly Anterior Infarction	Total
Initial QRS forces changed in direction (LBBB)	30 (19)	12 (7)	12 (10)	6 (1)	12 (5)	4 (3)	1	77 (45)
No change in direction of initial QRS forces (*not* LBBB)	0	0	21 (13)	27 (5)	2 (2)	1	0	51 (20)
Total	30	12	33	33	14	5	1	128

(In parentheses are those cases which are perfectly controlled, as defined in the text.)

tion resembling left bundle branch block, and it is possible to recognize infarction from the QRS complexes in such cases despite the prolongation.

METHODS AND MATERIALS

The 128 cases used in this study were collected from a number of different hospitals by examining all tracings in cases which had been coded as either bundle branch block or other types of ventricular conduction disturbance. In over 90 per cent of the tracings, standard and unipolar limb lead and six conventional precordial V leads were available; in the remaining tracings three limb leads and at least three precordial V leads had been recorded. The interval between the tracing with normal conduction and the tracing with QRS prolongation was less than two years in all cases and less than six months in 80 per cent of the cases. In sixty-five of the 128 cases, or about half of the series, one or more tracings with normal conduction had been recorded after the tracing showing QRS prolongation and, in forty-four of these, tracings with normal conduction had been recorded both before and after the tracing with QRS prolongation. These sixty-five cases represent perfectly controlled cases, because other QRS complex abnormalities which might have accompanied the onset of the QRS prolongation could be identified. The conclusions of this study are based upon analysis of these sixty-five cases, the remaining instances being used to support the conclusions and to indicate the frequency of the phenomena studied.

To simplify the presentation, the cases are grouped according to the characteristics of the QRS complex in the control tracing, as shown in Table 1. The QRS criteria used for defining the electrical location of myocardial infarction have been described elsewhere.[6] Clinical and pathologic data were not conveniently available in most instances and no broad clinical or pathologic correlations are attempted. The effects of the QRS prolongation on the T waves or on the ventricular gradient were not studied. The vector methods used have been described previously.[7,8]

RESULTS

Amount of Prolongation of QRS Complex. It is generally believed that in bundle branch block the QRS complex becomes prolonged by .04 second. This is based upon the demonstration that trans-septal spread of excitation in the dog takes about .04 second. In the 128 cases of the present study the average QRS prolongation over the duration of the QRS complex in the control tracing was .05 to .06 second. However, of considerable interest was the frequency with which the amount of prolongation exceeded this figure. Thus one third of the cases showed .07 second or more prolongation, and one fifth of the cases (twenty-three) showed more than .08 second prolongation. The largest amount of prolongation in this series was .13 second in a patient receiving quinidine. In none of the cases was there evidence that the prolongation developed gradually or in stages. The degree of prolongation appeared to remain fairly constant in a given patient, rarely varying over .01 to .02 second in those instances in which a sufficient number of tracings were available to make such an evaluation possible. In cases of intermittent or paroxysmal block there tended to be the same amount of prolongation each time. The amount of prolongation seemed unrelated to either the QRS duration or the type of QRS complex in the control tracing. Thus patients with infarction showed the same distribution of degrees of prolongation as patients with normal QRS complexes in the control tracing.

It has been said that when the QRS complex

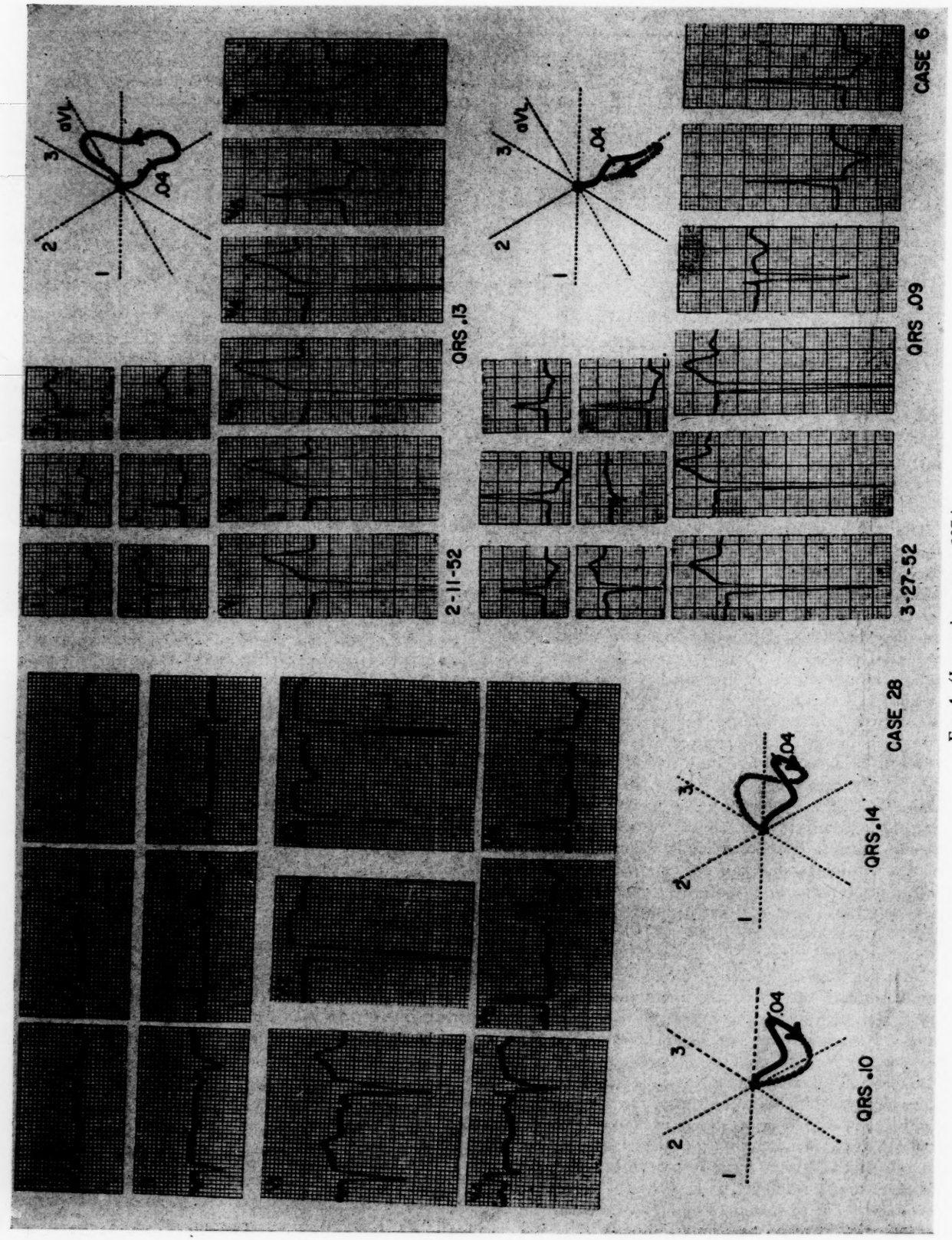


FIG. 1. (Legend on page 837.)

exceeds .14 second in left bundle branch block, left ventricular hypertrophy is present in addition to the bundle branch block.[9] To be sure, hypertrophy of the septum might prolong transseptal spread of excitation and thereby produce greater than usual QRS complex prolongation in the presence of left bundle branch block. However, in the present series of cases QRS complex prolongation of .16 second and greater was by no means restricted to cases showing left ventricular hypertrophy in the control tracing.

Instances of QRS prolongation of only .01 to .02 second have been described in cases of tachycardia[10] and following myocardial infarction,[6] and gradual beat-to-beat prolongation of the QRS complex by increments of less than .01 second has been described.[2,11–13] It can be concluded that conduction disturbances in the human subject may be associated with all degrees of QRS prolongation from less than .01 second to more than .13 second. To separate intraventricular block into an "incomplete block," when the QRS interval is prolonged by .02 second, and "complete block," when it is prolonged by .04 second, is to leave unexplained QRS prolongations of .06 or .08 or more second; and nearly half of all instances of what is called left bundle branch block fall into these latter categories.

Differentiation of Left Bundle Branch Block from Other Causes of QRS Prolongation of Leftward Type. It is generally accepted that during normal ventricular conduction the first .02 to .03 second of the QRS complex is written by electrical forces generated from the left ventricle. This has been demonstrated experimentally[14,15] and cogent evidence of it exists in clinical electrocardiography. For example, for myocardial infarction to produce Q waves in the electrocardiogram the infarct must have affected the first region of the ventricles to generate electrical forces, and it is well known that such infarcts lie mostly if not exclusively in the left ventricle. Excitation enters the left ventricle via the left bundle branch and therefore the left bundle branch can be considered responsible for the first QRS electrical forces generated by the heart during normal ventricular conduction. When the left bundle is blocked, excitation now enters the ventricles via the right bundle, and some region of the right ventricle will be the first to generate QRS electrical forces. The electrical force will necessarily have a different direction under these circumstances than when the left ventricle was the first to become excited.

Therefore, in a given case with left ventricular conduction disturbance, the only way to prove rigorously that it was due to left bundle branch block, short of histologic examination of the bundle, is to show that with the onset of the conduction defect the initial forces of the QRS interval were changed in direction. For complete proof one must, if possible, also demonstrate that the initial QRS forces returned to the preblock direction with disappearance of the conduction defect. This is necessary in order to rule out the possibility that infarction was the cause of the change in direction of initial QRS forces when QRS prolongation took place. On the other hand, if the initial QRS forces were not altered in direction or magnitude with the onset of the QRS prolongation it must be concluded that excitation entered the left ventricle normally and left bundle branch block cannot have been the cause of the prolongation.

One of the most important and unexpected findings in the present study was the high incidence of cases in which no change was revealed in the direction of initial QRS forces when QRS prolongation developed. Fifty-one, or more than a third of the cases in this series, were of this type. The two cases shown in Figure 1 illustrate this. It can be seen that there is no change in the initial part of the QRS loop in either case. From the "pattern" point of view this means that there is absolutely no difference in the contour of the first .03 to .04 second of the QRS complexes on any of the twelve leads when the tracing with QRS prolongation is compared with the control tracing. As shown in Table 1, QRS deformity of infarction was present in the control tracing in thirty of these fifty-one cases. The next highest incidence was seen in cases classified from the control tracing as left ventric-

FIG. 1. Two cases illustrating absence of change in initial QRS forces when QRS prolongation develops. The unlined part of the QRS loop indicates directions of instantaneous QRS vectors during the first .04 second of the QRS interval, and it can be seen that this portion of the loop is exactly the same during QRS prolongation and during normal ventricular conduction in both cases. From a "pattern" point of view this is best seen in lead aV_L of Case 6 because the early instantaneous vectors are relatively perpendicular to the axis of this lead. The control deflections in both cases are typical of left ventricular "strain," although a strictly anterior infarction cannot be confidently ruled out in Case 6. The QRS loops were constructed from the conventional limb lead tracings in all figures.

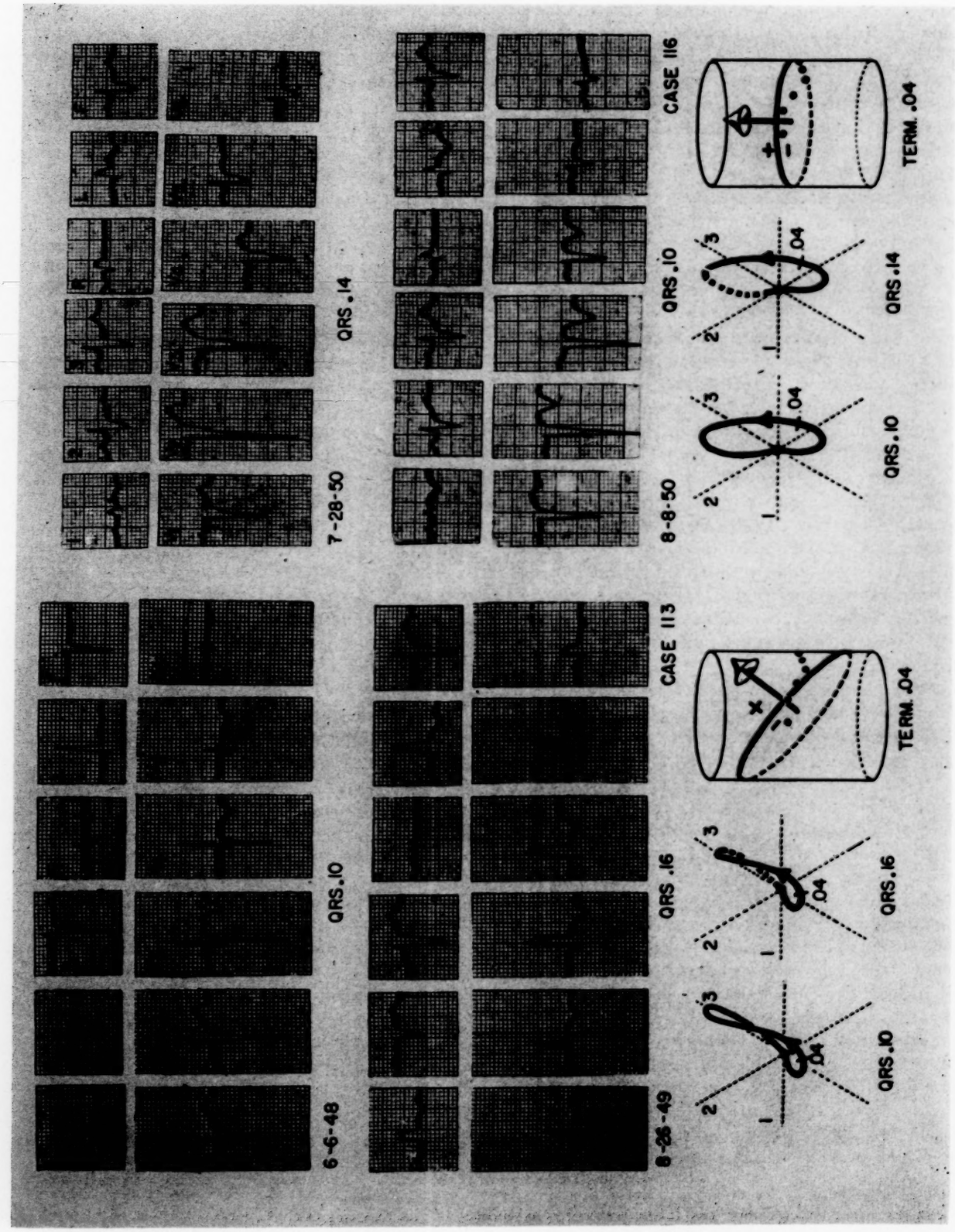


FIG. 2 (Legend on page 839.)

ular "strain." On the other hand, none of the thirty cases in which there were normal QRS complexes in the control tracing were of this type.

These cases are important in clinical electrocardiography for two reasons. First, they indicate that perhaps a third of the cases of QRS prolongation classified by current criteria as "left bundle branch block" are not in fact due to this entity. Many suggestions have been made in the literature that "focal" or "parietal" or "peri-infarction" block can cause QRS prolongation resembling left bundle branch block.[16–19] The present study provides the first objective proof that mechanisms other than bundle branch block can produce QRS prolongation in the human subject. Second, it has long been thought that infarction could not be recognized from the QRS complexes in the presence of left ventricular conduction defects. However, since the initial QRS forces are not changed in direction with this type of prolongation, the QRS complex deformity produced by infarction should still be recognizable in spite of the prolongation.

Left Ventricular Conduction Defects in Cases with QRS Complex Deformity of Infarction in Control Tracing. As shown in Table 1, there were fifty-three cases in the series which showed QRS complex deformity of myocardial infarction in the control tracing. In twenty-three of these, ten of which were perfectly controlled, a change was noted in the direction of the initial QRS forces when QRS prolongation took place, and left bundle branch block can be considered the cause of the prolongation in these cases. However, in thirty cases no change was noted in direction or magnitude of the initial QRS forces when prolongation developed, and the block must have been distal to the left bundle branch in these cases.

What is the cause of this type of QRS prolongation following infarction? It was shown previously that the electrical forces generated during the last .03 to .04 second of the QRS interval are often altered in direction by myocardial infarction with little or no prolongation of the QRS interval.[6] The terminal vectors become directed nearly opposite to the direction of the initial vectors of the QRS cycle. It is believed that an alteration in the direction of subendocardial spread of excitation is responsible for this conduction defect, the myocardial layers overlying the infarct becoming the last to generate QRS forces. This would explain why the terminal QRS vectors are relatively opposite in direction to the initial QRS vectors. In anterolateral infarction, for example, while the initial vectors are directed rightward and inferiorly (producing a Q_I, Q_L and precordial Q waves), the terminal vectors point leftward and superiorly (producing an R_I, S_2 and S_3). Control tracings in the two cases in Figure 2 illustrate this terminal vector alteration of anterolateral infarction.

It can be seen in the cases in Figures 2 and 3 that the terminal forces retain this direction when QRS prolongation of the type under discussion takes place in the presence of infarction. This suggests that the factors responsible for the abnormal terminal force direction in the control tracing may also be responsible for the QRS prolongation that later develops in certain of these cases. Two points of evidence support this possibility. One is that, in the terminal vector abnormality of anterolateral infarction, the terminal vectors are markedly leftward in direction. This, then, is the type of deformity which if prolonged would resemble a left ventricular conduction disturbance. As can be seen in Table 1, of the thirty cases of infarction that developed QRS prolongation of a leftward type without change of initial QRS forces, twenty-seven were cases of anterolateral infarction. Second, in a previous study it was found that in thirty-seven cases of anterolateral infarction without QRS prolongation less than half showed terminal vector alterations.[6] However, in the present series all but three of the twenty-seven cases of anterolateral infarction that later developed QRS prolongation showed this terminal vector alteration in the control tracing.

The particular direction which the terminal vectors are caused to take with infarction is a

FIG. 2. Two cases of anterolateral infarction with peri-infarction block in the control tracing. The initial QRS forces in the tracing with QRS prolongation have exactly the same direction as they have in the control tracing, as can be seen by comparing the initial parts of the QRS loops in each case. On the other hand, the terminal forces during prolongation (represented by the dotted parts of the QRS loops) are more anteriorly directed than they are in the control tracing. Spatial vector plots are drawn to indicate the spatial directions of these terminal forces during QRS prolongation. The black dots on the cylinders represent the relative locations of precordial electrodes on the chest.

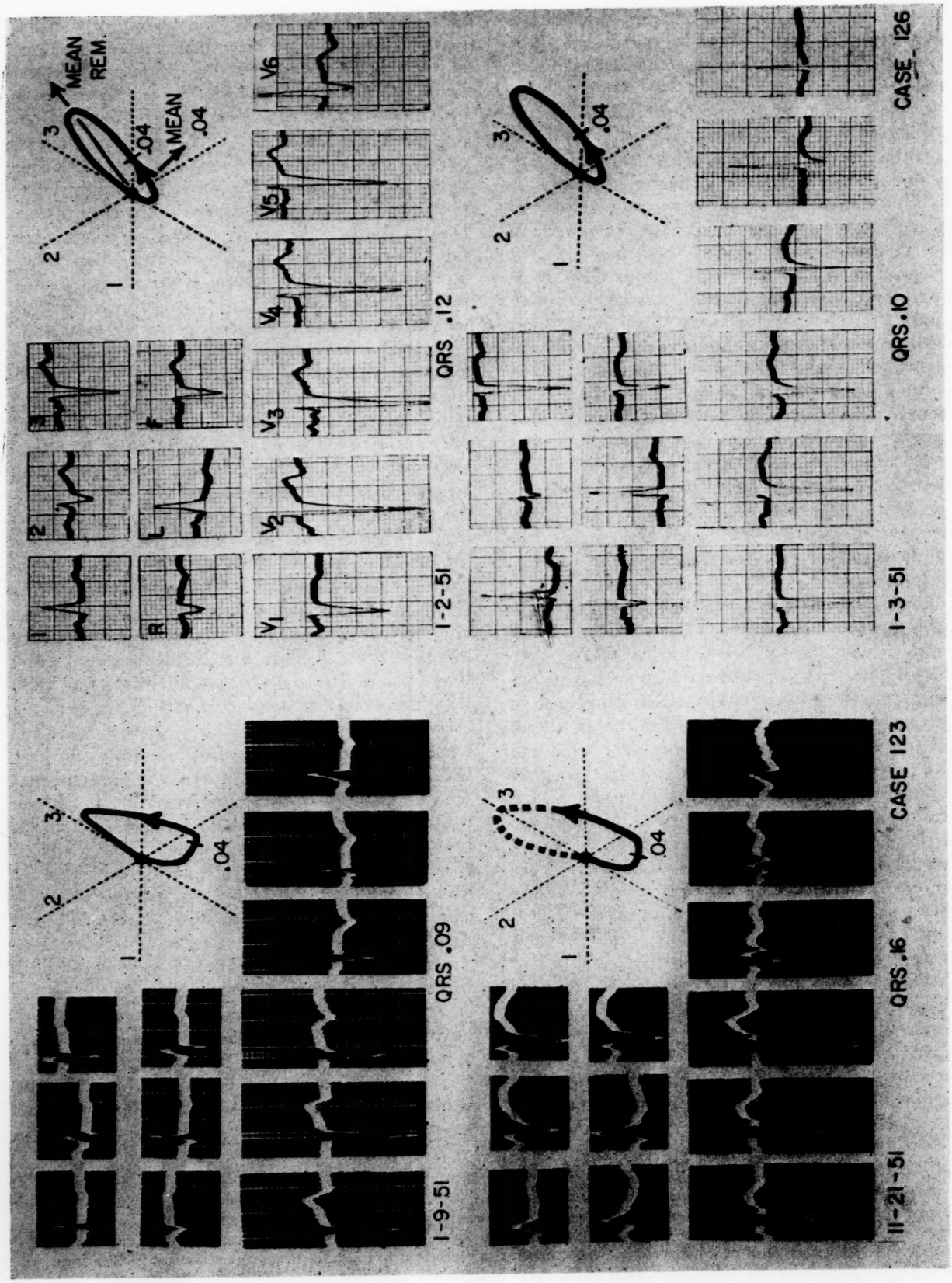


FIG. 3. (Legend on page 841.)

function of the electrical location of the infarct. Patients with anterolateral infarction have leftward and superiorly directed terminal forces; when QRS prolongation exceeds .12 second the QRS complexes closely resemble left bundle branch block, as illustrated by the cases in Figures 2, 3 and 4. On the other hand, when terminal vector alterations take place in diaphragmatic infarction they are directed rightward and inferiorly (opposite to the direction of the initial QRS vectors), producing an S_1, R_2 and R_3 on the limb leads; when QRS prolongation reaches .12 second in such cases, the QRS complexes closely resemble those of right bundle branch block. The terminal vector alterations of diaphragmatic infarction will be described in greater detail in a later paper concerned with the recognition of right ventricular conduction disturbances.

The sequence of QRS complex changes which may take place with anterolateral infarction was well demonstrated by Case 40-A in Figure 7 of a previous paper.[6] The sequence of QRS changes illustrated by this case is believed to take place in many cases of infarction: first, a conduction aberration at the site of the infarct produces a terminal vector alteration with little or no QRS prolongation; then, in a small percentage of cases, and for reasons that cannot be related to any recognized clinical or structural factor, greater degrees of QRS prolongation develop with no change in direction of the initial QRS forces and little if any change in the direction of the terminal forces.

In 1950 First, Bayley and Bedford presented a group of tracings with QRS prolongation resembling left bundle branch block in which Q waves were present in certain of the leads suggestive of infarction. They termed this "peri-infarction block," attributing the prolongation to a conduction defect in the region of the infarct.[19] It is practically certain that many of the cases in their report are examples of the type of QRS abnormality now under discussion, and the term "peri-infarction block" is particularly appropriate for it. However, First et al.[19] did not appreciate that the terminal vector alteration of peri-infarction block may take place with little or no prolongation of the QRS interval. Since the cause of the wide variation in amount of prolongation is not known, the term "peri-infarction block" should be used for the terminal vector alteration of infarction whether or not there is prolongation of the QRS interval. Several other authors have recognized that Q waves of infarction may be seen in certain cases with QRS prolongation resembling left bundle branch block, and in many cases the infarct has been demonstrated at autopsy.[18,23–26]

Another possible explanation for peri-infarction block should be mentioned. Perhaps all parts of the QRS complex deformity of infarction, the initial as well as the terminal vector abnormalities, are due to a conduction defect instead of to the death of units of generating tissue as is generally believed. The left bundle branch consists of two major divisions of fibers, an anterior division and a posterior division. During normal conduction excitation spreads simultaneously and with great rapidity through both divisions throughout the subendocardial layers of the left ventricle in the first .02 second of the QRS interval. An infarct in the distribution of one division would cause excitation to spread entirely through the other division. This would cause considerable alteration in the sequences of depolarization but little prolongation, accounting for the initial and terminal QRS complex deformity of infarction without QRS prolongation. Then, depending perhaps upon the area and depth of involvement of the conduction network by the infarct and its later fibrosis, various degrees of QRS prolongation would be produced.

Such an explanation would account for the stereotypy of the initial and terminal QRS com-

FIG. 3. Case 123 is an example of anterolateral infarction with peri-infarction block. In the tracing with QRS prolongation a Q wave is seen in lead I which was not present in the control tracing. As can be seen from the QRS loops this is due to a slightly more rightward direction of the initial QRS forces, attributable to a slight shift in the position of the heart such as might occur during the respiratory cycle. Note also that the terminal forces are more anteriorly directed in the tracing with QRS prolongation, producing shallow biphasic components of the S waves in the precordial leads. Case 126 illustrates how difficult the differentiation of left ventricular "strain" from anterolateral infarction with peri-infarction terminal force directions may sometimes be: the Q waves in leads I and aV_L are not long enough to be diagnostic of infarction; the angle between the mean .04 vector and the mean of the remaining QRS forces is at the upper limits of normal; no QRS evidence is present of hypertrophy to support the diagnosis of "strain," nor are the precordial ST-T contours typical of this; finally, QRS prolongation without change in the direction of initial QRS forces, such as is shown here, may take place in either syndrome.

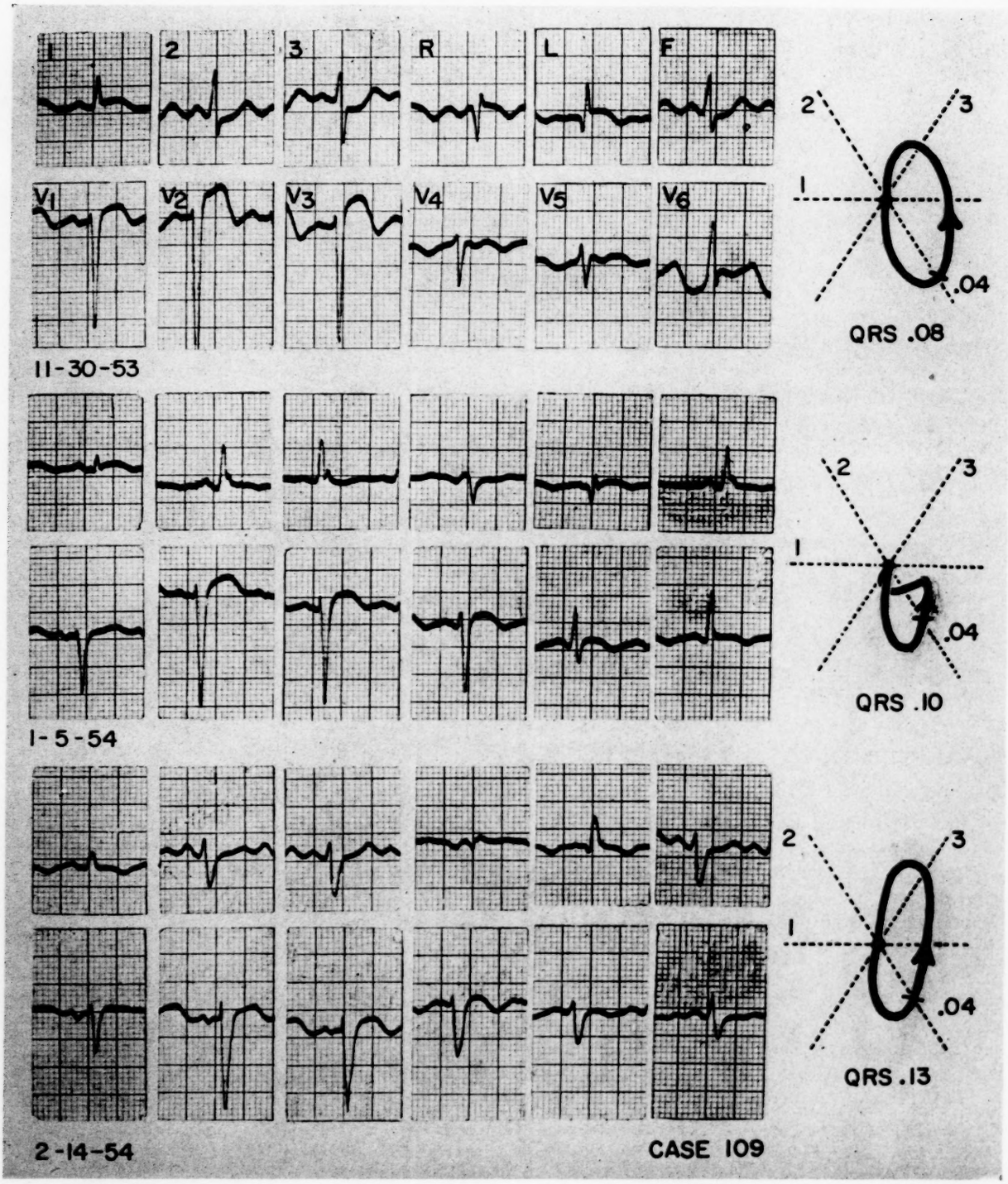


FIG. 4. Sequences of QRS changes in anterolateral infarction. In the first tracing anterolateral infarction with peri-infarction block is present, because both the initial and terminal QRS forces are abnormal and opposite to one another in direction. In the second tracing the terminal force changes have vanished but no change occurs in the direction of initial QRS forces. (The tiny Q wave in lead I is due to a barely measurable change in direction of these forces, as can be seen by comparing the take-off of the QRS loops for the two tracings.) In the third tracing, peri-infarction block has returned, this time with QRS prolongation superimposed but with no change in the initial QRS forces.

plex deformities of infarction seen clinically; there are, after all, but two main categories of infarction from an electrical point of view, one anterior and the other diaphragmatic. In addition it would explain why certain cases of infarction proved at autopsy may have shown no QRS complex deformity. If this explanation were correct it would suggest that peri-infarction block is not likely ever to occur in the absence of deformity of the initial QRS electrical forces. This would be of importance in clinical electrocardiography because, now that peri-infarction block can be recognized in the clinical tracing, the question arises as to whether or not the terminal deformity can ever occur as the sole QRS abnormality of infarction. So far the authors have not found a case of peri-infarction block proved both electrically and pathologically in which no deformity of the initial forces of the QRS complex was present. However, proved cases of infarction with control tracings are rare, and further search will be necessary to settle this possibility.

The Q Wave in Lead I *in Left Ventricular Conduction Disturbances with Infarction.* A broad Q wave in lead I in the presence of QRS prolongation resembling left bundle branch block is generally accepted as diagnostic of infarction of the septum with left bundle branch block. The Q wave is attributed to septal infarction in the following way: With the septum inert electrically the right-to-left spread of excitation across the septum which is characteristic of left bundle branch block cannot take place. Under these circumstances the first region of the heart to become excited is the free wall of the right ventricle. The electrical forces generated from this region are directed rightward, producing the Q wave in lead I.

Several shortcomings are present in this explanation. In the first place, many cases of extensive septal infarction have been reported in which left bundle branch block with Q_1 did not occur.[47] In one series of 102 cases of septal infarction proved at autopsy several instances of QRS prolongation were noted but only one was considered to be due to left bundle branch block.[18] Furthermore, cases of left bundle branch block with a Q wave in lead I have been reported in which no infarction had taken place.[20–22] Finally, in only four cases with QRS prolongation and a Q_1 have preblock tracings been available as controls, and in two of these the Q wave was present prior to the block.[20]

Among the 128 cases of left ventricular conduction disturbances in this series were twenty-nine cases with measurable Q wave in lead I in the tracing with QRS prolongation. Five of these showed no evidence of infarction in the control tracing, and in none of these did the Q_1 exceed .02 second. The remaining twenty-four cases all showed the QRS complex deformity of infarction in the control tracing. In fifteen of these the Q wave in lead I was .03 second or more in the tracing with QRS prolongation. Case 113 in Figure 2 and Case 123 in Figure 3 illustrate this. It can be concluded that the Q wave in lead I must be .03 or more to be itself indicative of infarction in the presence of QRS prolongation.

However, the important feature of these twenty-four cases is that in none was there any change in the direction of the initial QRS vectors when QRS prolongation developed. In other words, the same Q waves were present prior to the block in all cases. This means that the mode of entrance of excitation into the ventricles was not altered when QRS prolongation took place, and therefore left bundle branch block cannot have been the cause of the QRS prolongation. Peri-infarction block was responsible for the QRS prolongation in all these cases.

Further, among the twenty-four patients with infarction in the control tracing in whom left bundle branch block was proved to be the cause of the QRS prolongation, none acquired a Q_1 with the block. Six of these twenty-four cases were examples of anterolateral infarction with Q waves in lead I of the control tracing. In all six the Q waves in lead I vanished when left bundle branch block developed.

In summary, while, theoretically, infarction of the septum might account for a Q_1 in the presence of left bundle branch block, it is an exceedingly rare event, and peri-infarction block is a much commoner cause of such an electrocardiographic pattern.

Criteria for Differentiating Peri-infarction Block from Left Bundle Branch Block. Any tracing resembling left bundle branch block, but with Q waves in certain leads similar to those seen in infarction, should raise the question of peri-infarction block. However, confident differentiation of the two is often difficult because the change in direction of initial QRS forces that takes place with the development of left bundle branch block somewhat resembles the change in direction that accompanies anterior infarction.

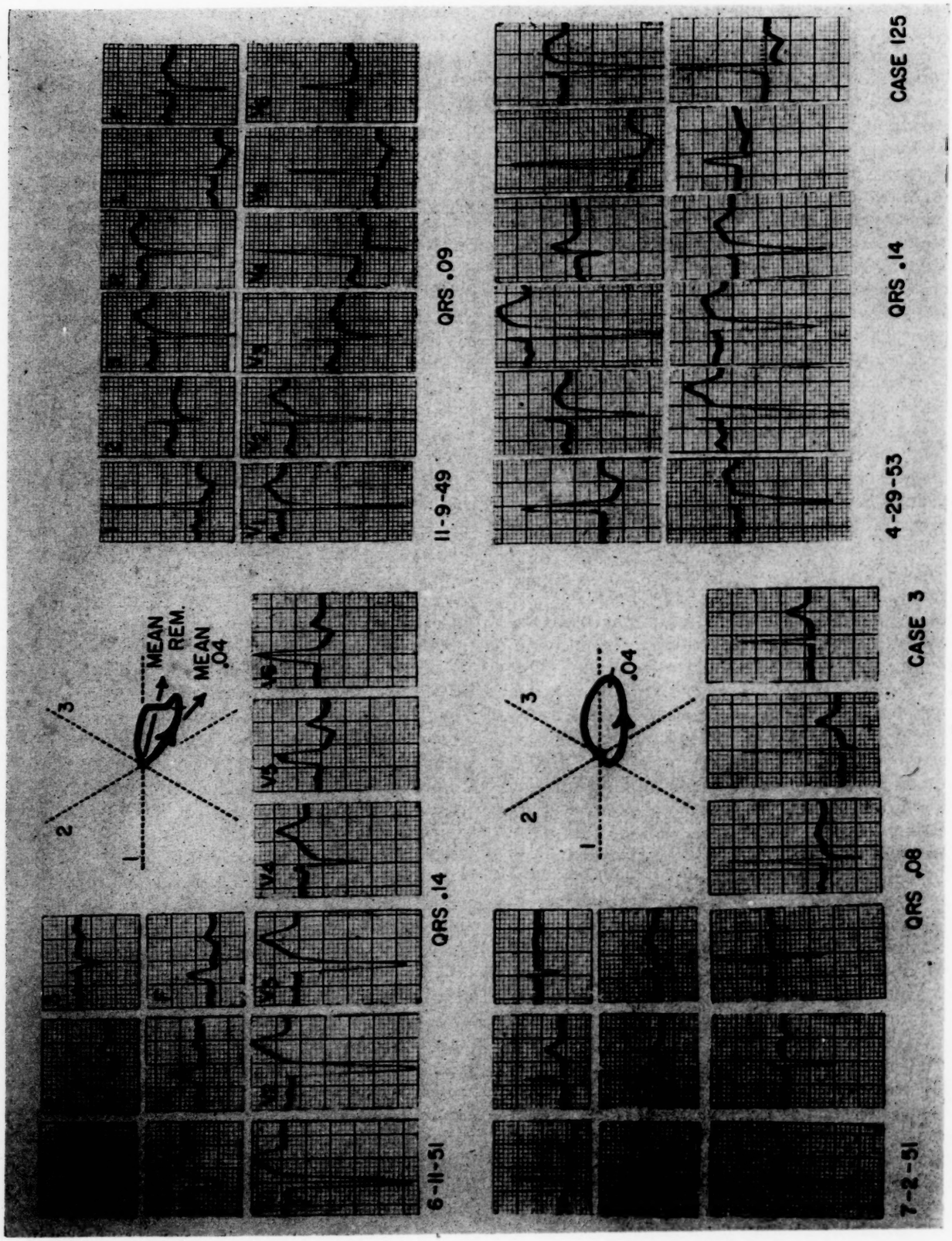


FIG. 5. (Legend on page 845.)

The initial QRS forces are caused to point more posteriorly and the R waves at V_1 to V_3 become considerable smaller, as illustrated by Case 3 in Figure 5. However, the differences between the two causes of prolongation which have been seen in the present study suggest criteria that may be helpful in differentiating the two conditions. It should be pointed out, however, that the criteria are based upon a small number of cases, and a much larger series with control tracings and pathologic confirmation will be necessary before these criteria can be considered completely reliable.

It was pointed out earlier that in this series a Q wave in lead I exceeding .02 second occurred only in peri-infarction block and never in left bundle branch block. Other features which differentiated peri-infarction block from left bundle branch block in this series are the following: (1) Q waves of less than .02 second at V_6 were seen in two cases of left bundle branch block with normal control tracings. Nine cases were seen in which this Q wave measured .03 second or more and in all nine cases the QRS prolongation was due to peri-infarction block. (2) It has often been thought that with left bundle branch block the initial positivity of the QRS complexes in the precordial leads may be lost. This proved to be uncommon. Among the seventy-seven cases of proved left bundle branch block in the present series, initial R waves were present from V_1 through V_4 in 45 per cent; absent R waves at V_1 only were noted in 35 per cent and absent R waves at V_1 and V_2 in 15 per cent. Thus in only 5 per cent of cases was the initial positivity lost as far over as V_3 and in none as far as V_4. To be sure, the initial R wave in left bundle branch block is characteristically small, and in a patient with marked obesity or anasarca it may be difficult to identify. In any event, seven patients with peri-infarction block were seen who showed loss of initial positivity to V_4 or beyond during QRS prolongation. (3) Fourteen cases with an initial R wave at V_1 of .03 second or more all proved to be examples of peri-infarction block with prolongation. (4) In left bundle branch block the amplitude of the initial R wave in the precordial leads may vary irregularly but in this series there were no instances in which it dwindled systematically in magnitude from V_1 to V_4. On the other hand, three cases of peri-infarction block with prolongation were seen in which such dwindling of the initial R wave from V_1 to V_4 took place.

It has been suggested that a certain type of notching of the broad R wave at V_6 is diagnostic of infarction in the presence of left bundle branch block. In the present series fourteen of the 128 cases showed this notching; half of these were examples of peri-infarction block but in the remainder no evidence of infarction was noted in the control tracing. Likewise, it has been suggested that a broad Q wave in aV_L is as valuable as a Q wave in lead I for differentiating infarction with block from uncomplicated left bundle branch block.[28] This proved not to be the case, for nearly as many cases of proved uncomplicated left bundle branch block showed such Q waves in aV_L as did cases of peri-infarction block.

So far the differentiation of left bundle branch block from peri-infarction block has been described in terms of the "patterns" of the QRS complexes on the various leads. A more objective and accurate method for studying these differences is the vector method. Since this method integrates the information of all the leads of the conventional tracing into a single measurement or groups of measurements, it often discloses relationships between electrical forces which are implicit but not easily seen in the "patterns" of the complexes on the various leads. Furthermore, it prevents errors of interpretation due to unusual anatomic positions of the heart or to respiratory shifts of the heart which have been shown occasionally to produce Q waves in lead I in uncomplicated left bundle branch block.[22]

The item that separated the largest number of cases of peri-infarction block from proved left bundle branch block in this series was the angle

FIG. 5. Case 3 is an example of left bundle branch block which subsequently became unblocked. It illustrates several features of left bundle branch block: (1) The initial QRS forces are changed in direction, becoming leftward and slightly posteriorly directed as compared with the direction during normal ventricular conduction. (2) Usually no change takes place in the direction of the mean QRS axis when bundle branch block develops; in this case the mean QRS axis has almost exactly the same horizontal direction with and without block. (3) The angle between the mean .04 vector and the mean of the remaining QRS forces rarely exceeds 45 degrees. Case 125 is an example of QRS prolongation that took place gradually over a four-year period as left ventricular hypertrophy progressed.

between the mean vector during the first .04 second of the QRS interval and the mean vector for the remainder of the QRS interval. When left bundle branch block occurs in a patient with a previously normal tracing, this angle is usually narrow. Among thirty cases of proved left bundle branch block with normal control tracings, the angle was less than 45 degrees in all but three, in two it reached 60 degrees and in one nearly 80 degrees. On the other hand, there were twenty-two cases in which this angle exceeded 100 degrees either in the frontal plane or in three dimensional space and all but two of these were cases of peri-infarction block. In these two cases the control tracing was within normal limits and there were no post-prolongation tracings; however, clinical data strongly indicated that infarction had accompanied or shortly preceded the onset of the QRS prolongation in both cases. Moreover, this angle was less than 60 degrees in only one of the remaining ten cases of peri-infarction block. In this case the initial QRS forces pointed rightward and superiorly, as if away from an anterodiaphragmatic electrical location of the infarct, but the terminal forces had the direction seen in cases of anterolateral infarction.

Measuring this angle should prove helpful in cases of QRS prolongation when the distribution of Q waves is suggestive but not diagnostic of peri-infarction block with prolongation. Indeed, it is the abnormal direction of the initial .04 vector that accounts for the Q waves and other abnormalities of the initial part of the QRS complex in infarction. The initial vector-terminal vector angle is simply a way of establishing the fact that the initial and terminal QRS forces are relatively opposite in direction, which is a basic characteristic of peri-infarction block.

Another valuable measurement for detecting peri-infarction block in tracings with QRS prolongation is the direction of the vector responsible for the last .04 second of the QRS interval, for it was frequently less posteriorly directed in peri-infarction block than in left bundle branch block. The reason for this may be that in normal ventricular conduction the last region of the heart to be depolarized is the posterior base of the left ventricle, generating markedly posteriorly directed electrical forces. In left bundle branch block this might still be expected to be among the last regions of the heart to be excited. On the other hand, in peri-infarction block the last region of the heart to be depolarized is presumably the epicardium overlying the infarct and this would be the high lateral and even anterior part of the left ventricle in anterolateral infarction. In thirteen cases of peri-infarction block the terminal QRS vector was either parallel with the frontal plane of the body or even slightly anteriorly directed, tending, it seems, to be more anteriorly directed in cases with greater degrees of QRS prolongation. This was manifested in the precordial lead QRS complexes by shallow terminal S waves or even terminal R waves in V_1 to V_3, as illustrated by Cases 113 and 116 of Figure 2, where the directions of the terminal vectors are plotted, and in case 123 of Figure 3. In none of the cases of proved left bundle branch block was this direction of the terminal vector seen. This type of terminal force deformity of infarction in cases resembling left bundle branch block has also been noted by Cabrera.[27]

It must be remembered that when an electrical force is markedly leftward the transitional plane for the vector forms a pathway across the chest which is more or less parallel with the distribution of precordial lead electrode locations. If in addition the vector is relatively parallel with the frontal plane of the body, the transitional pathway will run right through these precordial lead positions. Under these circumstances slight differences in the placement of the precordial electrodes from one tracing to another in a given patient may change them from the area of relative positivity (and writing positive deflections) to the area of relative negativity (and writing negative deflections). This is illustrated diagrammatically in Figure 6 and explains why consecutive tracings in patients with peri-infarction block may on one occasion show terminal R waves and on another shallow terminal S waves in the precordial leads. It also demonstrates one of the shortcomings of the electrode locations now generally accepted for recording precordial leads.

Left Ventricular Conduction Defects in Cases with Left Ventricular "Strain" in Control Tracing. In another group of cases no change in initial QRS forces took place with the development of QRS prolongation. These are the cases with left ventricular "strain" in the control tracing (that is, mean spatial ST and T vectors relatively parallel with one another and nearly 180 degrees from the direction of the mean spatial QRS vec-

tor with a QRS duration of .11 second or less*). Of thirty-three cases in this group twenty-one showed no change in initial QRS forces on developing QRS prolongation; therefore left bundle branch block cannot have been the cause of QRS prolongation in these twenty-one cases. This is illustrated by Cases 6 and 28 in Figure 1 and Case 126 in Figure 3.

Three explanations for the prolongation in these twenty-one cases are possible, and each of the three explanations may be responsible for prolongation in certain cases.

1. It is possible that the control tracing represents incomplete left bundle branch block, the QRS prolongation being due to the development of complete left bundle branch block. Under these circumstances no change in initial QRS forces would occur because they are already abnormally directed due to the left bundle branch conduction defect. It has often been suggested that the left ventricular "strain" tracing is in certain cases nothing more than incomplete left bundle branch block. Similar ST-T contour abnormalities and the same slight QRS prolongation occur, and differentiation is often quite difficult.[3,29,30] One difference is believed to be the presence of a Q wave in lead I in left ventricular strain and its absence in incomplete left bundle branch block.[20,29] In the present series fifteen of the thirty-three cases called left ventricular strain had such Q waves in the control tracing, but only two of these were among the twenty-one cases which showed no change in the direction of initial QRS forces when the QRS became prolonged. This suggests that several of the latter were examples of incomplete left bundle branch block rather than left ventricular strain.

However, this cannot be the explanation in all twenty-one cases. In the first place, half of these cases had QRS intervals of .09 second or less and one of only .07 second in the control tracing. The diagnosis of incomplete left bundle branch block generally requires a QRS duration of over .09 second.[10] But perhaps the most important evidence against considering many of these cases of incomplete block is the observation that while two-thirds of the thirty-three cases in this group reverted to the pattern called left ventricular strain after the period of QRS prolongation, not a single case was noted to revert to a normal QRS pattern and ST and T pattern. It seems likely that if complete left bundle branch block

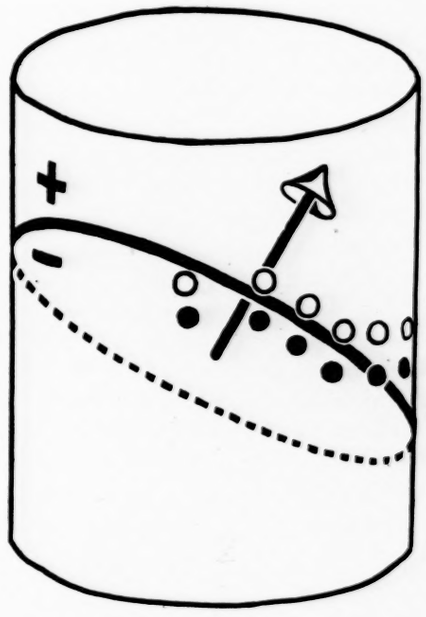


FIG. 6. Scheme illustrating that slight differences in the location of precordial electrodes can produce marked changes in the deflections written by an electrical force when that electrical force is directed leftward and parallel with the frontal plane of the body. The cylinder represents the human chest; the closed dots are the normal precordial electrode locations, and the open dots represent electrode locations which are slightly superior to these. It can be seen that the transitional pathway which divides the chest into a superior area of relative positivity (where upright deflections are written) and an inferior area of relative negativity (where inverted deflections would be written) is relatively parallel with the locations of the precordial electrodes. If the solid dots are used for the precordial leads, negative deflections will be written at V_2 through V_4; while if the open dots are used, positive deflections will be written at these electrode positions.

* The diagnosis by electrocardiogram of "strain" properly requires that there be evidence of hypertrophy with increased QRS amplitude. However, the amplitude of QRS complexes is difficult to evaluate when the body build and body size of the patient are not known, as was true in these cases. Therefore, all cases with ST and T vectors relatively opposite to the QRS vector were considered "strain" in this study, regardless of amplitude of the QRS complex, provided no QRS deformity of infarction appeared in the tracing. This definition is much looser than is desirable.

could so commonly become "unblocked," incomplete left block should also occasionally become "unblocked." Not only was this not seen in the present series but a subsequent search among over three hundred cases fulfilling the criteria cited for left ventricular "strain" failed to disclose a single case in which the "strain" tracing was preceded or followed within a reasonably short period by a tracing with normal ST-T contours, a shorter QRS interval, and differently directed initial QRS forces to prove that the contours were due to a conduction defect.*

Furthermore it is difficult to find such cases in the literature on this subject. Experimental observations and rare clinical cases have been presented in which beat-to-beat prolongation of the QRS interval took place leading to complete bundle branch block, thereby demonstrating that there can be intermediate degrees of QRS prolongation leading to complete left bundle branch block.[2,11–13] However, three cases of intermittent and alternating blocks in the present series and in those published by others have never shown such gradual prolongation; it is likely that the intermediate stages of prolongation are too unstable to produce a fixed block of that degree. A number of cases have been reported in which normalization of the "strain" pattern occurred following successful treatment of arterial hypertension. In those cases in which the interval between the two tracings was sufficiently short to rule out the possibility that the QRS changes were due to changes in heart size, there is no change of initial QRS forces when the ST-T contours returned to normal; therefore the abnormality cannot be attributed to bundle branch block.[30–34] Segers has published a series of tracings in which slight prolongation of the QRS interval was seen in the ventricular deflections associated with premature auricular contractions.[35,36] Some or these deflections closely resemble the left ventricular strain deflections. However, in view of the prematurity of the QRS complex it is possible that refractoriness of one or another region of the ventricles accounts for these bizarre complexes and they may not be examples of bundle branch conduction defects. These arguments are not intended to mean that there is no such condition as incomplete left bundle branch block but simply that it must be very rare and that it has not yet been proved to be a cause of a stable form of QRS prolongation of less than .12 second in man.

2. In certain of the twenty-one cases the increase in QRS duration can be attributed to progressive left ventricular hypertrophy. Under these circumstances the initial QRS forces would not be expected to change in direction as the QRS complex interval became prolonged. Case 125 in Figure 5 is an example. In this patient with severe arterial hypertension annual tracings over a four-year period showed that the QRS complex was increasing in amplitude and duration as the illness progressed and no sudden change occurred in the direction of the initial QRS forces. It is likely that hypertrophy was the cause of prolongation in this case. How many others among the twenty-one cases in which QRS prolongation developed by this mechanism is not known because clinical information was incomplete for many of them. Hypertrophy may be expected to prolong the QRS interval slightly by increasing the thickness of the ventricular wall. However, probably a much more important factor is the diffuse myocardial fibrosis commonly seen in severe hypertrophy.

It has been suggested that hypertrophy is the cause of the QRS prolongation in most cases that are called left bundle branch block.[37] However, in many of the tracings published to demonstrate this a marked change occurs in the direction of the initial QRS forces with the development of the QRS prolongation. This means that the mode of entrance of excitation into the left ventricle was altered and a conduction disturbance in the bundle must have taken place in these cases.

3. A third possible explanation of the QRS prolongation in certain of these cases is myocardial infarction. The directions of initial and terminal QRS forces in the cases of left ventricular "strain" with left axis deviation is very similar to the directions seen in peri-infarction block of anterolateral infarction. Furthermore the ST segment and T wave changes of "strain" closely resemble those in subendocardial infarction and in diffuse myocardial fibrosis due to chronic coronary artery disease.[38–41] Finally, unusually wide initial vector–terminal vector angles are often seen in cases fulfilling the criteria for left ventricular "strain." In five of the twenty-one cases now under discussion this angle exceeded 90 degrees, which is near the range

* The authors would like to acknowledge the assistance of Mr. Edward Frohlich of the University of Maryland Medical School in this search.

considered diagnostic of anterolateral infarction with peri-infarction block. In the remaining cases the angle was considerably smaller. Case 126 in Figure 3 illustrates this difficulty; the angle is wide, there are small Q waves in leads I, aV_L and V_6, yet none of these features is marked enough to be diagnostic of infarction. It is possible that several of the cases called "strain" were actually instances of anterolateral infarction, and the QRS prolongation was related to peri-infarction block. The resemblance between the two syndromes is so close that only more extensive well controlled clinical-pathologic-electrocardiographic correlation studies will clarify the criteria for differentiating them.

COMMENTS

It has been shown that perhaps a third of cases of what is ordinarily called left bundle branch block are due to delay in the left ventricle distal to the main branch of the left bundle. The evidence for this lies in the demonstration that the electrical forces generated during the first .02 to .04 second of the QRS interval are not altered either in magnitude or direction when QRS prolongation takes place in these cases. The mechanism of this type of conduction delay has already been discussed. In the remaining two-thirds of the cases in this series the initial QRS forces were changed in direction with the onset of prolongation. The conduction defect must be at the site of entrance of excitation into the left ventricle in these cases, and it is therefore appropriate to call them left bundle branch block.

The most widely held explanation of the mechanism of spread of excitation in left bundle branch block postulates that excitation reaches the left ventricle by spreading from right to left across the septum, regaining passage in the left bundle branch below the site of the block.[20,45,46] The present study indicates that this is not altogether the case in bundle branch block in man. A simple physical analogy will explain the basis for this conclusion.

If a number of electrical forces are generated from the center of a volume conductor, the net measurement of the electrical activity from these electrical forces will remain the same no matter what the sequence in which they are generated. This is shown diagrammatically in Figure 7. Here three electrical forces of different magnitudes and directions, A, B and C, are shown being generated from the center of a volume conductor. The dotted line represents the axis of a galvanometric lead for recording the electrical forces. For simplicity, assume that each force is generated suddenly and subsides suddenly, generating a square wave, and that they all have the same duration. On the right are shown the

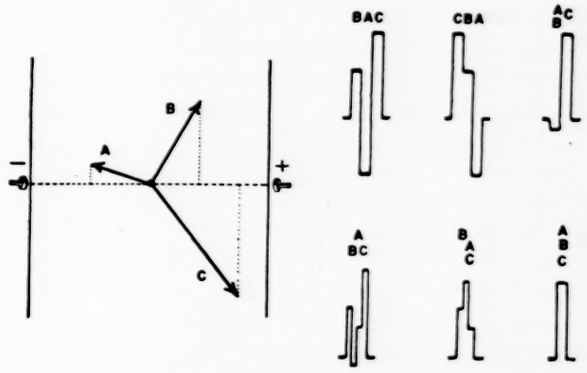


FIG. 7. Scheme illustrating that the net enclosed area of an electrocardiogram deflection is not altered when the sequence in which electrical forces are generated is altered.

deflections which would be written by the galvanometer for various sequences and combinations of simultaneity in which the three forces might be generated, the letters above the deflections indicating the particular sequence for that deflection. It can be seen that no matter what the sequence in which they are generated, or even if they are all generated at once, the net area of the deflection remains the same.

If left bundle branch block were solely due to a change in the sequence in which the various regions of the heart are activated, the net area of the QRS deflection on any lead should remain the same as it was during normal ventricular conduction. This has never been observed to be the case. The net area of the QRS complexes is always increased significantly and often greatly by development of bundle branch block. This means that in left bundle branch block there is not only a change in the sequence of activation but that some additional alteration in the mode of excitation of the heart has taken place.

Excitation of the septum from right to left in left bundle branch block would produce a larger electrical force during the first .04 second of the QRS interval than was present with normal ventricular conduction.[45] However, the increase in net area of the deflection in left bundle branch block is not confined to the first .04 second. Furthermore, if conduction path-

ways were used for excitation of the left ventricle after this initial trans-septal excitation, the terminal QRS vector should have the same direction during left bundle branch block as it does during normal ventricular conduction. This is rarely seen, the terminal forces usually becoming more leftward and posteriorly directed during block.

Two explanations are possible for the increased net area of the QRS complex in left bundle branch block. One is that there may be some diffuse biochemical abnormality in the myocardium depressing conductivity throughout the Purkinje network or perhaps resulting in greater persistence of activation at each myocardial membrane. This is not likely to be the case in left bundle branch block. However, an alteration of this type is responsible for the QRS prolongation in certain cases of quinidine intoxication and hyperkalemia,[42] and it probably plays a part in the QRS prolongation of the agonal tracing and in hypothermia.[43,44]

The only other possible explanation, and the one that is believed to be responsible in conventional bundle branch block, is that the activation invades each region of the heart in a different direction than it does with normal ventricular conduction. Under these circumstances the resultant electrical activity from each region will be altered. This would mean that in left bundle branch block excitation never regains passage in the Purkinje network but spreads from the right ventricle by fiber-to-fiber conduction throughout the left ventricle. This mechanism of spread is of course much slower than when Purkinje fibre pathways are used. Perhaps this is the explanation for the wide variation in degree of QRS prolongation seen in the cases in this study.

Recent studies using intramural recording records have suggested that the subendocardium is electrically "silent" and does not contribute substantially to the QRS complex.[4,45] The explanation that has been offered for this finding is that the Purkinje network initiates activation by setting up myriads of "islands" of activation in the subendocardium. Excitation spreads concentrically from each "island," but not until the islands coalesce to form a bounded wave front is there resultant electrical activity which can be recorded in the electrocardiogram. If this were true, it might be conjectured that in left bundle branch block left ventricular depolarization no longer is initiated by the silent "islands" of activation but instead by a wave front spreading from the right ventricle. This would in part at least account for the greatly increased electromotive force that is recorded in left bundle branch block. However, it is well to remember that the demonstration of a "silent" subendocardium is an experimental finding and other investigators have not been able to confirm it.[15]

CONCLUSIONS

1. One hundred and twenty-eight cases of QRS prolongation to .12 second or more due to left ventricular conduction disturbances have been collected. In each case one or more tracings with normal ventricular conduction had been recorded either before or after (or both before and after) the tracings with QRS prolongation. This, then, appears to be the first controlled study of the effects of conduction defects on QRS electrical forces in man, the tracing with normal ventricular conduction serving as the control in each case.

2. The QRS interval was prolonged by .05 to .06 second over the control QRS duration in the average case. In twenty-three cases the QRS interval was prolonged by more than .08 second. To divide left bundle branch block into "complete" and "incomplete" depending upon whether or not the QRS duration exceeds .11 second is to leave unaccounted for this wide variation in QRS prolongation in the "complete" block cases. Evidence is presented which indicates that incomplete left bundle branch block (QRS interval prolongation to only .10 to .11 second due to a conduction defect in the left main bundle) must be exceedingly rare as a stable form of QRS prolongation and that it has not yet been proved ever to take place in man.

3. In one-third of the 128 cases no change in the direction or magnitude of the forces during the first .03 to .04 second of the QRS interval occurred with onset of the QRS prolongation. Therefore, left bundle branch block cannot have been the cause of the QRS prolongation in these cases. Half of the cases of this type have the QRS complex deformity of myocardial infarction in the control tracing. The QRS prolongation in these cases is shown to be related to peri-infarction block. QRS criteria for differentiating peri-infarction block with prolongation from left bundle branch block are outlined. Most cases of left ventricular conduction disturbance with a Q wave in lead I prove to be due to peri-infarc-

tion block with prolongation rather than to left bundle branch block with septal infarction, as is generally believed.

4. The other cases in which there had been no change in initial QRS forces when prolongation developed showed varying degrees of the left ventricular "strain" pattern in the control tracing. Further hypertrophy accounted for the prolongation in certain of the cases, and probably peri-infarction prolongation accounted for it in others. The similarity between left ventricular "strain" and anterolateral infarction with peri-infarction block is emphasized.

5. This study demonstrates that the objective principles of the control study can be brought to electrocardiographic research. The use of such methods in future electrocardiographic-pathologic correlation studies should lead to much more accurate and comprehensive electrocardiographic criteria for the recognition of myocardial infarction, conduction disturbances and many other syndromes. However, the scarcity of well controlled cases of this type makes it likely that some sort of cooperative study or central collecting group will be necessary for gathering this material.

Acknowledgment: We wish to thank Miss Clara V. King for her help in this study. The Directors of the Heart Stations of the following hospitals generously made their electrocardiographic files available to the authors; Georgetown University Hospital, Washington, D. C.; George Washington University Hospital, Washington, D. C.; Mount Alto Veterans' Hospital, Washington, D. C.; U. S. Public Health Service Hospital, Baltimore, Md.; Emory University Hospital, Atlanta, Ga.; Philadelphia General Hospital, Philadelphia, Pa.; Veterans' Hospital, Richmond, Va.; Walter Reed General Hospital, Washington, D. C.; U. S. Naval Medical Center, Bethesda, Md.; Strong Memorial Hospital, Rochester, N. Y.; Chicago Medical School, Chicago, Ill.; Presbyterian Hospital, Chicago, Ill.; Billings Hospital, Chicago, Ill.; West Side Veterans' Hospital, Chicago, Ill.; Henry Ford Hospital, Detroit, Mich.; Hines Veterans' Hospital, Hines, Mich.; the Pennsylvania Hospital, Philadelphia, Pa.

REFERENCES

1. Lewis, T. and Rothschild, M. A. The excitatory process in the dog's heart. *Phil. Tr. Lond.*, 206: 181, 1915.
2. Wilson, F. N. and Hermann, G. R. An experimental study of incomplete heart block. *Heart*, 8: 230, 1921.
3. Sodi-Pollares, D., Estandia, A., Soberon, G. and Rodriguez, M. I. Left intraventricular potential of the human heart. *Am. Heart J.*, 40: 650, 1950.
4. Kennamer, R., Bernstein, J. L., Maxwell, M. H., Prinzmental, M. and Shaw, C. W. Studies on the mechanism of ventricular activity. *Am. Heart J.*, 46: 379, 1953.
5. Coehlo, E. et al. Potentiales intracavitaire du coeur gauche de l'homme. *Arch. d. mal. du coeur*, 44: 961, 1951.
6. Grant, R. P. and Murray, R. H. The QRS complex deformity of infarction in man. *Am. J. Med.*, 17: 587, 1954.
7. Grant, R. P. and Estes, E. H. Spatial Vector Electrocardiography. Philadelphia, 1951. The Blakiston Co.
8. Grant, R. P. Spatial vector electrocardiography. *Circulation*, 2: 676, 1950.
9. Masters, A. M., Kalter, H., Dack, S. and Jaffe, H. J. Relation between bundle branch block and cardiac enlargement. *Am. Heart J.*, 20: 186, 1940.
10. Bain, C. W. C. Variable ventricular complexes in heart block. *Brit. Heart J.*, 3: 75, 1941.
11. Shearn, M. A. and Rytand, D. A. Intermittent bundle branch block, (figure 8). *Arch. Int. Med.*, 91: 448, 1953.
12. Segers, M., Kenis, J., Desruelles, J. and Enderle, J. Modifications de QRS lors du bloc A-V. *Acta Cardiol.*, 9: 123, 1954.
13. Sodi Pollares, D. et al. Estudio electrocardiográfico de los bloqueos incompletos de rama. *Arch. Inst. cardiol. México*, 18: 497, 1948.
14. Burchell, H. B., Essex, H. E. and Pruitt, R. D. Studies on the spread of excitation through the ventricular myocardium. *Circulation*, 6: 161, 1952.
15. Sher, A. M., Young, A. C., Malmgren, A. L. and Paton, R. R. Activation of the interventricular septum. *Circulation Res.*, 3: 56, 1955.
16. Hellerstein, H. K. and Katz, L. N. Electrical effects of injury at various myocardial locations. *Am. Heart J.*, 36: 184, 1948.
17. Alzamoro-Castro, V. et al. Parietal focal block. *Circulation*, 7: 108, 1953.
18. Myers, G. B., Klein, H. A. and Hiratzka, T. Correlation of electrocardiographic and pathologic findings in infarction of the interventricular septum. *Am. Heart J.*, 37: 720, 1948.
19. First, S. R., Bayley, R. H. and Bedford, D. R. Peri-infarction block. *Circulation*, 2: 31, 1950.
20. Sodeman, W. A., Johnston, F. D. and Wilson, F. N. The Q_1 deflection of the electrocardiogram in bundle branch block and axis deviation. *Am. Heart J.*, 28: 271, 1944.
21. Goldberger, E. Basic electrocardiographic patterns in left bundle branch block. *J. Lab. & Clin. Med.*, 30: 220, 1945.
22. Lapin, A. W. and Sprague, H. B. Respiratory movement as a factor in production of Q_1 in left bundle branch block. *Am. Heart J.*, 35: 962, 1948.
23. Dressler, W., Roesler, H. and Schwager, A. Myocardial infarction with left bundle branch block. *Am. Heart J.*, 39: 217, 1950.
24. Moll, A. and Lutteroti, T. Significance of the

$R_1S_2S_3$ electrocardiographic pattern. *Ztschr. f. Kreislaufforsch.*, 40: 737, 1951.

25. Gmachl, E. Über Elektrokardiogramme mit überwiegend negativen Ausschlagen in Standardableitungen. *Cardiologia*, 20: 250, 1952.
26. Sodi-Pollares, D. and Rodriguez, M. I. Unipolar leads at the septal surfaces in bundle branch block complicated by myocardial infarction. *Am. Heart J.*, 43: 27, 1952.
27. Cabrera, E. and Friedland, C. Ventricular activation in left bundle branch block with infarct, a new sign. *Arch. Inst. cardiol. México*, 23: 441, 1953.
28. Rosenman, R. H., Pick, A. and Katz, L. N. Electrocardiographic patterns and localization of intraventricular conduction defects. *Am. Heart J.*, 40: 845, 1950.
29. Wilson, F. N., Rosenbaum, F. F. and Johnston, F. D. Interpretation of ventricular complex of the electrocardiogram. *Advances Int. Med.*, 2: 30, 1947.
30. Boyer, N. H. and Hewitt, W. L. Electrocardiogram in hypertension before and immediately after sympathectomy. *Am. Heart J.*, 40: 1, 1950.
31. Doyle, A. E. Electrocardiographic changes in hypertension treated by methonium compounds. *Am. Heart J.*, 45: 363, 1953.
32. Leishman, A. W. D. The electrocardiogram in hypertension. *Quart. J. Med.*, 20: 1, 1951.
33. Isberg, E. M. and Peet, M. M. Influence of splanchnicectomy on the heart in hypertension. *Am. Heart J.*, 35: 567, 1948.
34. White, P. D. Regression of cardiac insufficiency due to hypertension after sympathectomy. *Arch. d. mal. du coeur*, 39: 390, 1946.
35. Segers, M. Two components of preponderance and of intraventricular block. *Acta Cardiol.*, 8: 129, 1953.
36. Segers, M. Intermittent intraventricular block. *Arch. d. mal. du coeur*, 46: 814, 1953.
37. Rasmussen, H. Electrocardiogram in aortic insufficiency. *Acta med. Scandinav.*, 118: 385, 1944.
38. Weinberg, S. L., Reynolds, R. W., Rosenman, R. H. and Katz, L. N. Electrocardiographic changes in myocardial fibrosis. *Am. Heart J.*, 40: 745, 1950.
39. Littman, D. Ventricular strain and ventricular hypertrophy. *New England J. Med.*, 241: 363, 1949.
40. Yu, P. N. G. and Stewart, J. M. Subendocardial infarction with special reference to electrocardiographic changes. *Am. Heart J.*, 39: 862, 1950.
41. Levine, H. D. and Ford, R. V. Subendocardial infarction. *Circulation*, 1: 246, 1950.
42. Personal observations.
43. Bigelow, W. G., Lindsay, W. K. and Greenwood, W. F. Hypothermia. *Ann. Surg.*, 132: 849, 1950.
44. Sarajas, H. S. S. Observations on electrocardiographic alterations in hibernating hedge hog. *Acta physiol. Scandinav.*, 32: 28, 1954.
45. Sodi-Pollares, D. et al. Activation of left ventricular wall in dog's heart in normal conditions and in left bundle branch block. *Am. Heart J.*, 49: 587, 1955.
46. Smith, A. L., Kennamer, R. and Prinzmetal, M. Ventricular excitation in experimental bundle branch block. *Circulation Res.*, 2: 221, 1954.
47. Roesler, H. and Dressler, W. An electrocardiographic pattern of infarction of the interventricular septum. *Am. Heart J.*, 34: 817, 1947.

Loud Presystolic Sounds over the Jugular Veins Associated with High Venous Pressure*

WILLIAM DOCK, M.D.
Brooklyn, New York

We recently stumbled onto the fact that loud sounds could be recorded during atrial systole over the jugular veins of patients with large P waves and elevated pressure in the right atrium. This led us to review the previous reports on auscultation over the jugular veins and finally to the conclusion that this phenomenon had escaped the notice even of those who had an intense interest in venous pulses and sounds. The published jugular phonograms do not show any presystolic sounds similar to those we have obtained, although faint sounds due to atrial systole have been recorded repeatedly in the last four decades.

Our first observation was the result of noting huge presystolic ballistocardiographic waves, headward and rightward, in a man with mitral stenosis, mild failure of the right side of the heart and a P-R interval of 0.26 seconds. (Fig. 1.) Routine precordial phonocardiograms showed a faint apical first sound, ascribable to the long A-V interval, together with classical presystolic murmurs and loud pulmonic second sounds. (Fig. 2.) No gallop could be detected over the precordium but as there were large spiked P waves, giant jugular *a* waves and minimal venous collapse in either systole or early diastole, the possibility of a tight tricuspid stenosis was considered. Phonograms taken from the right jugular bulb exhibited a loud, split presystolic sound. (Fig. 2.) The first and second sounds, faint in this area, were quite loud just below the clavicle where no presystolic sound was recorded. (Fig. 2.) Later, catheterization established the presence of tricuspid stenosis with normal pulmonary arterial pressure, and angiocardiograms showed a large right auricle which failed to empty in twenty seconds. In brief, seeing huge presystolic gallop waves in the ballistocardiograms with no gallop in routine precordial sound traces, led to recording a jugular gallop sound and establishing the diagnosis of tricuspid disease in a patient long considered to have pure mitral stenosis.

The next day the same sound was recorded in a young woman returning for study after a mitral valvulotomy. Here, too, the gallop was not apparent just caudal to the right clavicle but the first and second sounds, together with a loud systolic murmur, also could be heard over the jugular vein, so that there was a local gallop rhythm not audible over the precordium. (Fig. 3.) In this patient there was no functional stenosis or insufficiency of the tricuspid valve since the jugular pressure falls sharply after the *c* and *v* waves. (Fig. 3.) Thus we learned that the presystolic gallop over the jugular bulb was not pathognomonic of tricuspid stenosis. Within a few days opportunity arose to seek this sound in two patients with congenital heart disease who had previously been catheterized and known to have high right auricular pressure without mitral or tricuspid disease. Both had a presystolic gallop of great intensity, recorded only over the jugular bulb. (Fig. 4.) Failure to record anything but faint sounds or inaudible vibrations from the jugular bulb of normal subjects or from patients with left ventricular failure and normal venous pressures, forced us to conclude that a loud presystolic sound limited to the veins was pathognomonic of right atrial hypertension.

The main facts concerning the first twelve subjects with loud presystolic jugular sounds are

* From the Department of Medicine, State University of New York College of Medicine, New York City, Brooklyn, New York. This work was supported by Grant H 1250 from the Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Bethesda, Maryland.

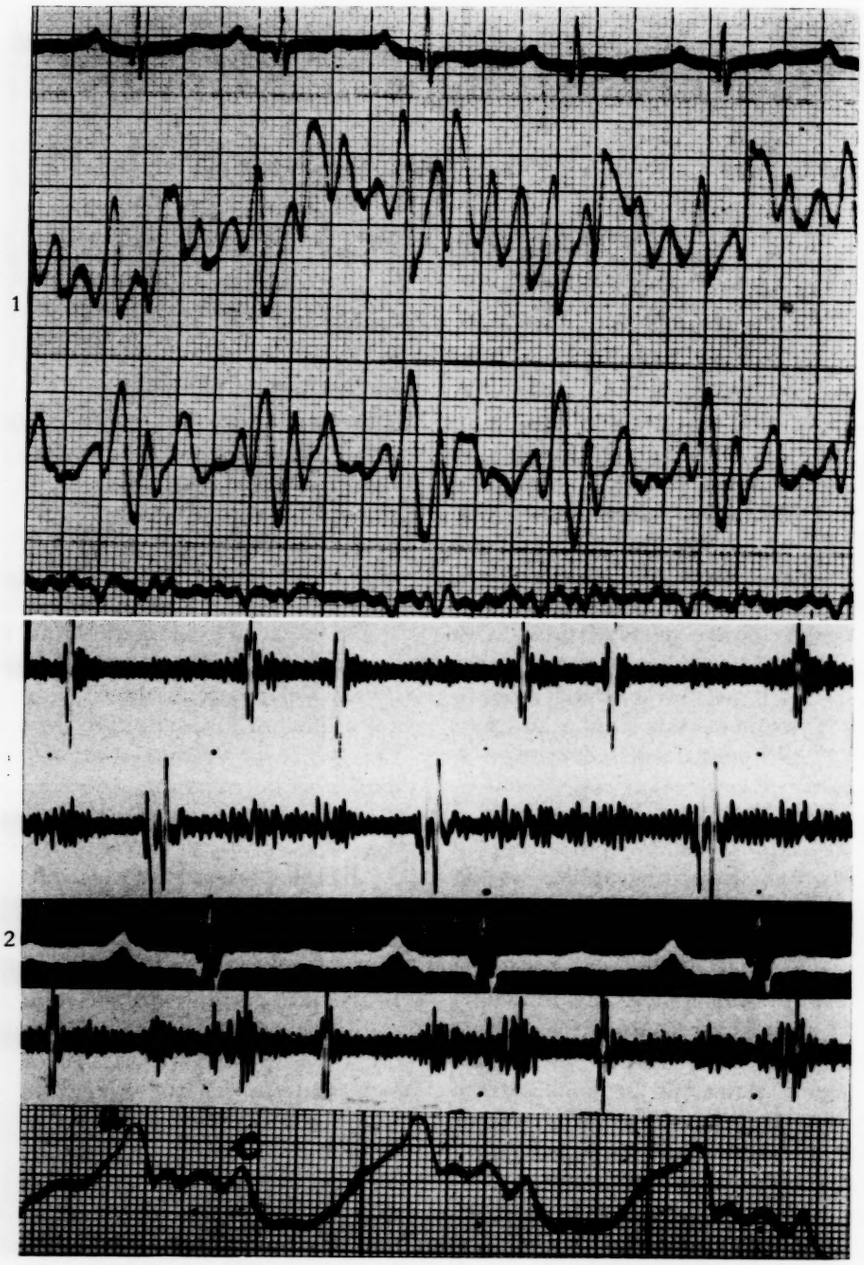


FIG. 1. Case 1. Tricuspid and mitral stenosis. From above downward, the electrocardiogram, head-foot, lateral and dorsoventral ballistocardiograms; upward is headward, rightward and backward. A rightward then leftward presystolic complex is the outstanding feature, but in the first and last beats a headward wave nearly as large as the notched systolic J wave precedes the rightward motion by 0.06 seconds. The following footward wave is seen in other beats.

FIG. 2. Case 1. From above downward, the sounds in the first right interspace, sternal border; sounds over right jugular vein; electrocardiogram; sounds at apex; jugular pulse. The bifid presystolic sound, loud above the clavicle, is inaudible just below it.

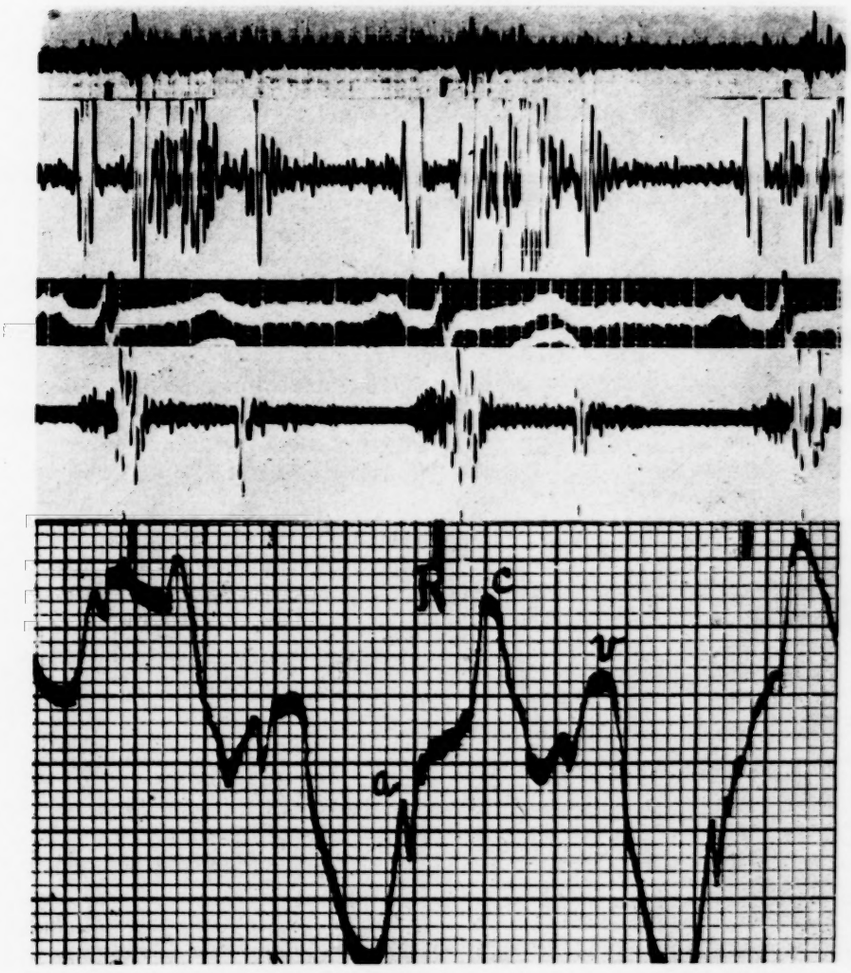


FIG. 3. Case 2. Mitral stenosis. Sounds in aortic area; over right jugular vein; electrocardiogram; sounds at apex; jugular pulse with black bar showing position of R waves recorded in these beats. Discussion in text.

shown in Table 1. In four cases the peak of the *a* wave fell very near the presystolic sound but in two cases it preceded the sound by 0.04 to 0.06 second and in five cases a reached its peak 0.04 to 0.07 second after the onset of the sound. When large presystolic ballistocardiographic waves occurred, headward or rightward motion usually began with the sound and reached a peak 0.02 to 0.05 second later. Cases 1 and 12, with tricuspid stenosis and P-R intervals over 0.25 second, had very large presystolic waves, which occurred much later than in those without tricuspid stenosis.

When ausculting over the jugular veins one may hear triple sounds or even four sounds, if the second sound is widely split. However, in some subjects with loud presystolic sounds above the clavicle either the first sound or, as in our first case, both normal sounds are inaudible in this area. Then the presence of a presystolic sound is realized only by timing with the carotid pulse. While presystolic jugular sounds do not occur in those with auricular fibrillation, loud systolic murmurs, not heard over the precordium, may be present with tricuspid insufficiency or, as in Case 2 (Fig. 3), when the valve is not physiologically insufficient and the jugular pulse curve is within normal limits.

In several cases the presystolic sound was loud above the sternal notch and over the left jugular vein; in others it was present over both jugular veins but not over the trachea. It was recorded with subjects in recumbent and in sitting positions, and a microphone with a small bell was pressed lightly on the neck and pointed at a slight angle, medially and caudally. Firm

pressure or the weight of an unsupported microphone may abolish the auricular gallop and accentuate the second sound in this area.

COMMENTS

During the nineteenth century physicians listened to the hum in the jugular area to estimate the severity of anemia. Discussions of venous sounds were frequent and sometimes rather warm. Careful comparisons were made of the phlebogram and the hums and sounds over the veins.[1] Some of these students of venous phenomena were also intensely interested in gallop rhythm but we have failed to find any mention of a loud presystolic jugular gallop. Nor have we found it in the writings of Lian and his colleagues who have stressed the value of auscultation in the suprasternal notch and in the first intercostal spaces.[2] Groedel, in his monograph on the venous pulse, did not refer to such a venous gallop,[3] nor were any examples found in Groedel and Miller's paper on acoustic phenomena in the neck.[4]

TABLE 1*

Case	A (1st Presystolic)	B (sec.)	C (sec.)	D (sec.)	E (sec.)
1	1 to 2.5	0.10	0.06	0.11	H—0.16; R—0.22
2	1 to 1	0.10	0.08	0.14	none
3	1 to 3	0.06	0.08	0.12	none
4	1 to 1	0.12	0.04	0.14	R—0.16
5	1 to 1.5	0.10	0.03	0.14	H—0.14; R—0.12
6	1 to 2	0.16	0.04	0.12	none
7	1 to 2	0.14	0.06	0.08	R—0.16
8	1 to 1.3	0.12	0.08	0.14	none
9	1 to 1	0.09	0.06	0.16	H—0.16
10	1 to 2	0.10	0.06	0.14	R & H—0.14
11	1 to 2	0.20	0.04	0.18	R, H & B—0.20
12	1 to 3	0.15	0.05	0.15	H—0.23; R—0.20

* Data on cases from which loud presystolic jugular sounds were recorded. All were adults under fifty years old. Patients in cases 1, 2, 4, 6 and 12 had mitral stenosis; 9 and 10, pulmonic stenosis; 3, tetralogy of Fallot; 5, patent ductus; 7, primary pulmonary hypertension; 8, large interventricular septal defect, and 11, severe rheumatic carditis. Column A, relative intensity of first sound and presystolic sound; B, interval from onset of P to onset presystolic sound; C, duration of presystolic sound; D, interval from P to peak of jugular a wave, and E, interval from P to peak of headward (H), rightward (R) or backward (B) waves of the ballistocardiogram.

A faint fourth sound has been heard and recorded from the precordium of many normal and diseased subjects. Similar small undulations in presystole are seen in Groedel and Miller's jugular phonocardiograms[4] from normal subjects; no loud presystolic sounds occurred in any of their eight subjects with acquired or congenital valvular disease. Only one of their cases (Case 23[4]) shows a jugular sound in presystole comparable with but fainter than the first sound in the same trace. This patient had no heart failure or valve lesion. All these fourth sounds, like our loud sounds, occur 0.12 to 0.16 second after the onset of the P wave.

A fourth heart sound is regularly recorded from the esophagus at the level of the auricles[5,6] but it is a faint sound, begins as early as 0.03 second after the origin of the P wave and is no louder in a subject with heart disease than it is in a healthy subject. Fourth sounds, presumably recorded from the upper precordium, are shown in diagrams of the heart sounds from five of eleven subjects with congenital aortic stenosis and from four of ten subjects with pulmonic stenosis reported by Reinhold and Nahas.[7] No fourth sounds are indicated in their diagrams based on phonocardiograms from many other congenital cardiac subjects, and in none of their cases do the fourth sounds compare in intensity with the murmurs or the first or second sounds of the same subject.

In contrast with the apparent lack of early or recent accounts of jugular sounds in atrial systole, comparable in loudness with the first heart sounds, is the single phonocardiogram published in 1914 by de Meyer and Gallimaerts.[8] This shows a single cycle from a subject of unstated age and physical status with a very tall *a* wave in the jugular phlebogram and a presystolic jugular sound louder than either the first or second sound. This lonely figure is a classic, reappearing in a textbook[9] and a monograph.[10] Josué and Godlewski[11] had reported hearing triple sounds over the jugulars of many normal subjects. They used the auricular sound in recognizing the nature of cardiac arrhythmias and thus stimulated the Belgian study which was cut short by the invasion of 1914. It is remarkable that no one has been stimulated by their widely circulated tracing, and none of those who made later studies published evidence of an atrial sound as loud as the first sound. Since the atrial wave in the jugular pulse is more than twice as high as the ventricular systolic *c* wave in de Meyer and Gallimaert's graphs, it seems likely that their subject had right atrial hypertension.[8–10]

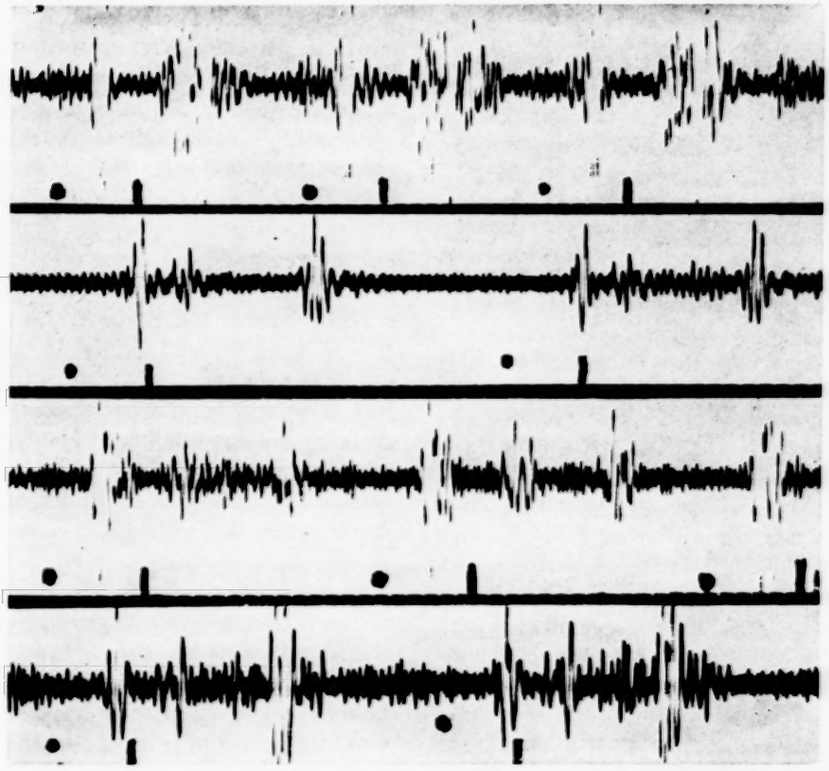


FIG. 4. Jugular sounds from Cases 5 (top), 6, 7 and 8 (bottom) with onset of P marked by dot, of R by bar, taken from electrocardiograms of same heart beats. Further data in Table 1. The presystolic sound is louder than the first sound in all cases, louder than the second sound in most cycles of all but Case 8.

The mechanism leading to a jugular presystolic sound seems to be the same as that causing the early systolic sound over the aorta or pulmonary artery, or over the peripheral arteries in subjects with high stroke volume. The fourth element of the first sound occurs when ejection into the great vessels begins, and it is loudest in those who have high stroke volume or high arterial pressures. It seems probable that a wave of blood entering the great arteries or veins can tense the fibers and set them into audible vibration. In the cases under consideration auricular ejection into the ventricle was resisted, either by high diastolic intraventricular pressure or, in Cases 1 and 12, by a tight tricuspid stenosis. This led to a reflux of blood into the great veins, the force of which was often sufficient to move the thorax headward and rightward more violently than it is moved by the ensuing ventricular systole. The vibration of the tensed veins causes a loud sound in the jugular areas, usually preceding the peaks of the jugular pressure wave and the ballistocardiographic waves. A delay in the sound over the left jugular vein as compared with the right can occasionally be noted. (Fig. 5.) This points to the vein itself as the point where the sound is produced. Apparently this phenomenon also occurs in cases of right heart failure at the time when jugular pressure rises abruptly with onset of ventricular systole. Here the sound accompanies the jugular *c* wave and is heard as a loud first sound. (Fig. 3, Case 2.) According to Calo,[10] this loud first sound may be heard not only over the jugular but over the cubital veins. It is noteworthy that the presystolic sound is rarely audible or recordable over the precordium, or even just across the clavicle from the point where it is of great intensity.

Sir James MacKenzie[12] observed "a clear, sharp sound preceding the first sound" over the jugular veins of a patient with tricuspid stenosis. He believed that the contraction of the hypertrophied right auricle "sent back a large wave into the jugular, and with such force that it caused the valves in the jugular and subclavian veins to close with a snap." The valves in the internal jugular and subclavian veins are

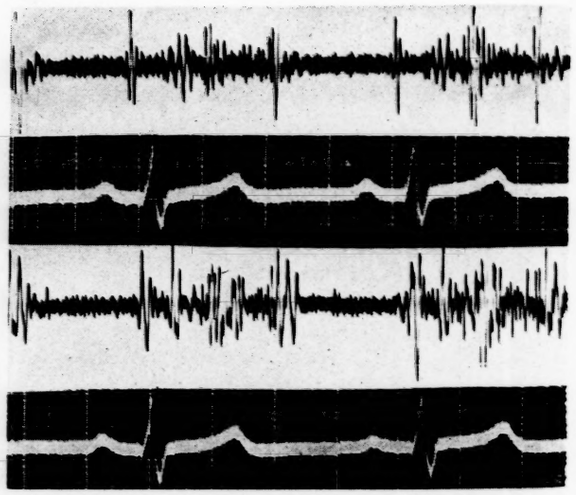


FIG. 5. From Case 10. The sounds over the right jugular vein (top) with the electrocardiogram below it; the sounds over the left jugular vein and the electrocardiogram below these. Note that the interval between the presystolic sound and the P wave is shorter; that between sound and R wave is longer on the right side than on the left.

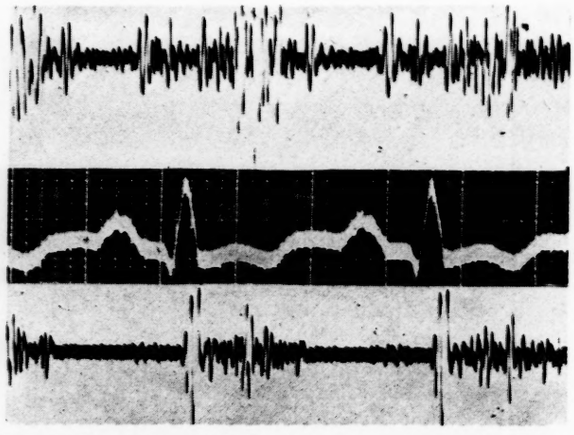


FIG. 6. From Case 10. Top, the sounds over the right jugular vein; bottom, over the right first interspace. Note that there is a second atrial sound in the jugular area; this occurs 0.08 second after the initial and louder presystolic sound.

described as occurring 2 to 3 cm. from the point where the veins enter the innominate veins, and it is therefore possible that the sounds actually arise in the valves rather than in the walls of the veins.

In one of the many traces taken above the clavicles of the patient in Case 1, and in one cycle of the patient in Case 2 (Fig. 3, last cycle), there was a brief sound occurring 0.08 second after the onset of the loud auricular sound. This was not present in all beats of the trace of the patient (Case 1) and was not noted in most of our subjects. In Case 9 it was noted in all traces, as shown in Figure 6. This sound was not quite as loud as the initial auricular sound and began about 0.09 second after that sound and 0.18 second after the onset of P. Its time relations and appearance are the same as those seen as a transient phenomenon in Case 1. These late complexes have the same relation to the P wave as the third element of the auricular sounds recorded from the precordium in cases of complete heart block. None of the hypothetical explanations for this late auricular sound (which has been recorded in the middle of ventricular systole) are convincing.[10] Its appearance in one of four cases with right atrial hypertension and presystolic gallop over the jugular veins adds to the mystery but perhaps may lead to its solution.

CONCLUSIONS

1. A loud presystolic gallop sound can usually be recorded from the areas over the jugular veins of patients with acquired or congenital heart disease when they have sinus rhythm and elevated levels of pressure in the right atrium.
2. This sound, maximal 0.10 to 0.16 second after the onset of P, is either absent or barely apparent in traces taken from the precordium, even in the first interspace.
3. This sound occurs close to the peak of the jugular *a* wave.
4. Patients with very loud fourth sounds from the jugular vein often have very large presystolic headward and/or rightward gallop waves in the ballistocardiogram.
5. These presystolic phenomena are believed to be due to a wave of blood moving violently centrifugally at the height of atrial systole when there is high pressure in the right ventricle at the end of diastole, or when there is tricuspid stenosis as in two of the patients in this series.

Acknowledgment: The author is grateful to Mrs. Samuel H. Boyer and to Drs. Francis M. Grandell and Mario del Fierro for recording jugular sounds on many control subjects and on Cases 3 to 12.

REFERENCES

1. POTAIN, P. C. E. Des mouvements et des bruits qui se passent dans les veines jugulaires. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 4: 3, 1867.
2. LIAN, C. and BENZECNY, I. El valor de la auscultacion del hueco suprasternal. *Prensa méd. argent.*, 37: 1709, 1950.
3. GROEDEL, F. M. The Venous Pulse and Its Graphic

Recording. New York, 1946. Brooklyn Medical Press.

4. GROEDEL, F. M. and MILLER, M. Studies on the acoustic phenomena over the vessels of the neck in the healthy and diseased. *Exper. Med. & Surg.*, 2: 193, 1944.
5. BENJAMIN, C. E. Ueber die Untersuchung des Herzens von der Speiseröhre aus. *Pflüger's Archiv. f. d. ges. Physiol.*, 158: 125, 1914.
6. TAQUINI, A. C. Exploracion del Corazon por Via Esofagica, p. 109–110. Buenos Aires, 1938. El Ateneo.
7. REINHOLD, J. D. L. and NAHAS, A. S. The rôle of auscultation in the diagnosis of congenital heart disease. *Am. Heart J.*, 47: 405, 1954.
8. DE MEYER, J. and GALLIMAERTS, V. Sur la photographie des bruits produits par le pouls veineux. *Ann. et bull. Soc. roy. d. sc. méd. et nat. de Bruxelles*, 72: 155, 1914.
9. DE WAELE, H. Traité de Physiologie Normale et Pathologique. Edited by Roget, G. H. and Binet, L. vol. 6, p. 474, Fig. 43. Paris, 1932. Masson et Cie.
10. CALO, A. Les Bruits du Coeur et des Vaisseauz. Fig. 218, p. 453. Paris, 1950. Masson et Cie.
11. JOSUÉ, O. and GODLEWSKI, H. L'auscultation du pouls veineux. *Bull et. mém. Soc. méd. d. hôp. de Paris*, 35: 401, 1913.
12. MACKENZIE, J. Diseases of the Heart, p. 230. London, 1908. Oxford University Press.

Pendular Motion of the Mediastinum*

PHILIP SAMET, M.D. *and* WILLIAM ANDERSON, M.D.

Miami Beach, Florida *Cumberland, Kentucky*

SINCE there is normally little or no shift of the mediastinal structures to either side during the respiratory cycle, the level of negative pressure developed must be approximately equal in the two pleural cavities. Any mechanism permitting development of unequal pressures in the two hemithoraces will result in pendular motion of the mediastinum unless this structure is "fixed" by prior disease. The existence of this phenomenon is well demonstrated in the literature on radiology.[1–6] Examples of such mechanisms will be presented in this paper together with a classification of the various types of mediastinal respiratory shift encountered.

METHODS AND MATERIALS

Pendular motion of the mediastinum was noted during fluoroscopic examination in twenty-one men. Nineteen subjects were hospitalized for pulmonary tuberculosis, one for left upper lobe bronchogenic carcinoma and the last for bilateral obstructive pulmonary emphysema with a left upper lobe bulla. In addition to routine history and physical examination, each patient was fluoroscoped to detect mediastinal shift with respiration. The technic recommended[2] by Rabin (placing a finger on the fluoroscopic screen on either side of the cardiac contour and watching for motion of both sides in the same direction during deep respiration) was employed.† Six foot chest films were taken in full inspiration and full expiration. Anteroposterior tomograms were obtained in many patients. Bronchoscopy and bronchospirometry with a Carlens tube[7] were performed in selected persons.

RESULTS

The fluoroscopic and radiographic data obtained in this study permit classification of the shift phenomenon into five types. The over-all results are shown in Table I.

Type I is illustrated by the three patients in group I. On inspiration the mediastinum is shifted toward the hemithorax which is the site of greater disease; on expiration this structure returns to a midline position. The pendular motion is detected on fluoroscopy but not on radiography because the shift is relatively slight.

Type II is illustrated by the thirteen patients in group II. Fluoroscopic observations are identical with those in group I but the shift is of sufficient magnitude to permit demonstration thereof on x-ray.

Type III is illustrated by the two patients in group III. Inspiratory mediastinal shift to the involved side with expiratory mediastinal shift to the opposite side is found on fluoroscopy and x-ray.

Type IV is illustrated by the two patients in group IV. In the presence of severe endobronchial stenosis, obstructive emphysema develops on the ipsilateral side. The mediastinum is midline on inspiration but is pushed into the contralateral hemithorax on expiration. In some instances the mediastinum may be displaced into the opposite side in both phases of respiration, more on expiration than on inspiration. These displacements are visible on fluoroscopy and x-ray.

Type V is illustrated by the patient in group V. With complete endobronchial stenosis the mediastinum is pulled into the diseased side during both phases of respiration, more on inspiration than on expiration. This may be noted both on fluoroscopy and x-ray.

Several points should be emphasized: (1) Resection of the apical-posterior segment of the left upper lobe in Case 6 (E. N.) and of the left upper lobe in Case 19 (G. G.) was followed by disappearance of the mediastinal shift. (2) Bronchospirometric studies producing variable data are shown in Table II. In two subjects of

† Normally the right and left cardiac borders move in opposite directions during the respiratory cycle. That is, in inspiration both borders move mesially as the mediastinal shadow narrows. During expiration the heart borders move laterally as the mediastinal shadow widens. With mediastinal respiratory shift, the right and left cardiac borders move in the same direction, either to the right or left, during both phases of the respiratory cycle.

* From the Medical Service, United States Public Health Service Hospital, Manhattan Beach, Brooklyn, New York.

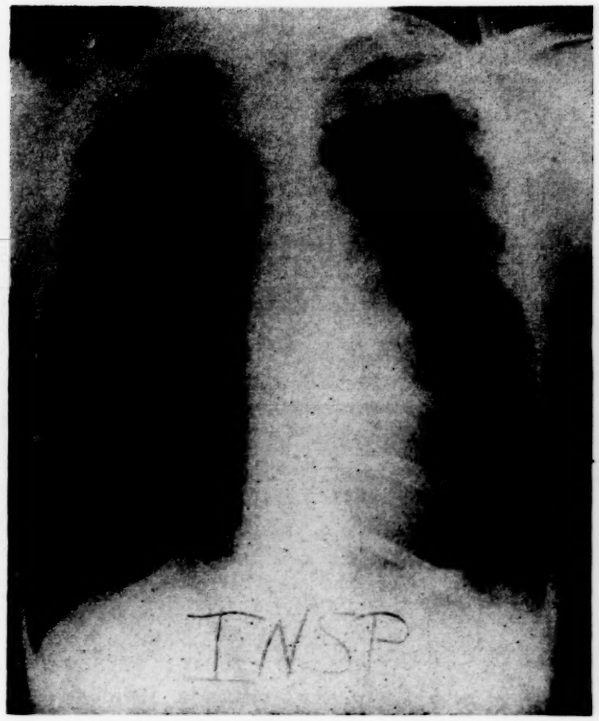


FIG. 1A. Inspiratory film of patient 4 (C. G.). The mediastinum is displaced into the left hemithorax.

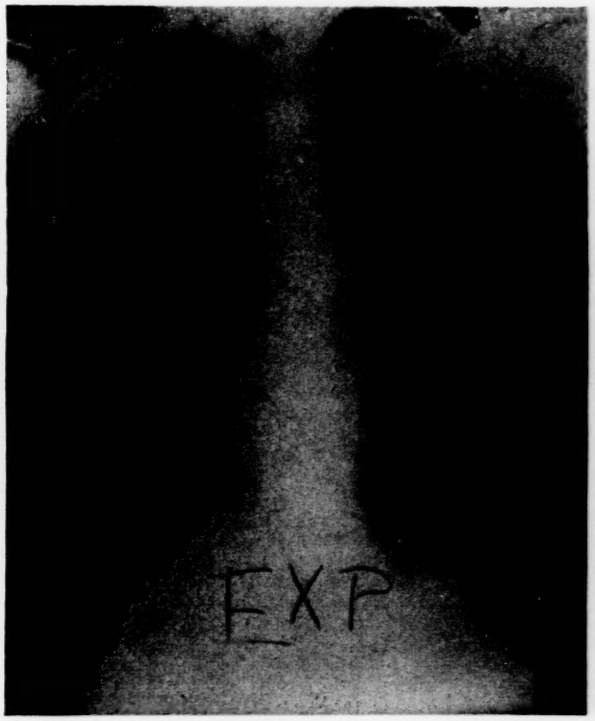


FIG. 1B. Expiratory film of patient 4 (C. G.). The mediastinum is midline.

group II (E. N. and S. L.), the partition of function between the two lungs was approximately that of normal. In a third subject in group II (J. I.), with an inspiratory shift to the right, the function of the right lung was decreased. In one patient in group I (J. T.), with an inspiratory shift to the left, the left lung exhibited moderate decrease in relative oxygen uptake and ventilation. Bronchospirometry was not completed successfully in two patients, Case 1 (T. L.) and Case 17 (F. T.). In both patients bronchoscopy revealed marked narrowing of the left upper lobe bronchus. The left main stem bronchus between the carina and the orifice of the left upper lobe bronchus was markedly foreshortened. As a result, inflation of the left sided balloon of the Carlens catheter repeatedly resulted in obstruction either of the left upper lobe or of the entire right lung. (3) An expiratory wheeze was noted on the side demonstrating obstructive emphysema in Cases 17 to 20. In each instance the involved lung failed to "lighten" in the expiratory film due to air trapping. (4) In Groups I and II limited respiratory excursions were frequently noted on physical examination on the side of the mediastinal inspiratory shift. (5) Spontaneous disappearance of the mediastinal shift was not observed during the course of the patient's illness in any instance.

The various types of mediastinal shifts encountered are illustrated in Figures 1 to 6.

COMMENTS

Westermark[5] and Schinz[1] have discussed the phenomenon of mediastinal respiratory shift, or pendular motion of the mediastinum, in some detail. Westermark has distinguished four stages of bronchostenosis produced by tumor, which are responsible for four types of mediastinal shift with respiration. In stage 1 slight occlusion of the main stem of the bronchus by tumor is described. The mediastinum is said to shift into the involved side on inspiration and to return to the midline on expiration. In stage 2 Westermark describes a mediastinal inspiratory shift into the involved side; on expiration this structure is pushed to the opposite side. In stage 3 the mediastinum is pushed into the normal chest on expiration and is either midline or displaced minimally into the normal side on inspiration. In stage 4 the involved bronchus is completely obstructed. The mediastinal structures are drawn into the dis-

TABLE I

FINDINGS IN TWENTY-ONE PATIENTS WITH MEDIASTINAL RESPIRATORY SHIFT

Case No. and Patient	Age (yr.)	Diagnosis	Tracheal* Shift	Bronchoscopy	Mediastinal Shift (Fluoroscopy and X-ray)	
					Inspiration	Expiration
Group I†						
1, T. L.	37	Far advanced pulmonary tuberculosis	Absent	Stenosis left upper lobe bronchus	To left side	Midline
2, L. K.	31	Far advanced pulmonary tuberculosis	To right side on inspiration; midline on expiration	.....	To right side	Midline
3, J. T.	32	Far advanced pulmonary tuberculosis	Absent	.....	To left side	Midline
Group II						
4, C. G.	30	Far advanced pulmonary tuberculosis	To left side on inspiration; midline on expiration	.....	To left side	Midline
5, A. B.	36	Moderately advanced pulmonary tuberculosis	Absent	Normal	To left side	Midline
6, E. N. Preoperatively	37	Moderately advanced pulmonary tuberculosis	To left side on inspiration; midline on expiration	Normal	To left side	Midline
Postoperatively		Resection apical posterior segment of left upper lobe	Absent	.....	Absent	Absent
7, S. L.	19	Far advanced pulmonary tuberculosis	To right side on inspiration; midline on expiration	Normal	To right side	Midline
8, A. S.	43	Far advanced pulmonary tuberculosis	Absent	Normal	To right side	Midline
9, J. I.	43	Far advanced pulmonary tuberculosis	Absent	.....	To right side	Midline
10, E. H.	46	Moderately advanced pulmonary tuberculosis	To left side on inspiration; midline on expiration	Stenosis left main bronchus	To left side	Midline
11, M. A.	27	Far advanced pulmonary tuberculosis	Absent	Normal	To right side	Midline
12, E. W.	44	Far advanced pulmonary tuberculosis	To left side on inspiration; midline on expiration	.....	To left side	Midline

TABLE 1 (*Continued*)

Case No. and Patient	Age (yr.)	Diagnosis	Tracheal* Shift	Bronchoscopy	Mediastinal Shift (Fluoroscopy and X-ray)	
					Inspiration	Expiration
13, J. C.	52	Far advanced pulmonary tuberculosis	Absent	Stenosis right upper lobe bronchus	To right side	Midline
14, J. H.	48	Far advanced pulmonary tuberculosis	Absent	Normal	To right side	Midline
15, J. Mc. G.	49	Far advanced pulmonary tuberculosis	Absent	Normal	To right side	Midline
16, B. A.	54	Far advanced pulmonary tuberculosis	Absent	.....	To left side	Midline
		Group III				
17, F. T.	54	Far advanced pulmonary tuberculosis	To left side on inspiration; midline on expiration	Stenosis left upper lobe bronchus	To left side	To right side
18, T. H.	47	Far advanced pulmonary tuberculosis	.....	Stenosis right upper lobe bronchus	To right side	To left side
		Group IV				
19, G. G. Preoperatively	53	Obstructive pulmonary emphysema; left upper lobe bulla	.....	.....	Midline	To right side
Postoperatively		Resection left upper lobe; three-rib thoracoplasty	.....	.....	Absent	Absent
20, E. T.	54	Obstructive pulmonary emphysema; far advanced pulmonary tuberculosis; right upper lobe sponge thoracoplasty	Absent	.....	Midline	To left side
		Group V				
21, J. P.	63	Left upper lobe squamous cell carcinoma	Absent	Occlusion left upper lobe bronchus	Pronounced shift to left side	Minimal shift to left side

* On physical examination.
† Mediastinal respiratory shift not seen on x-ray in group I patients.

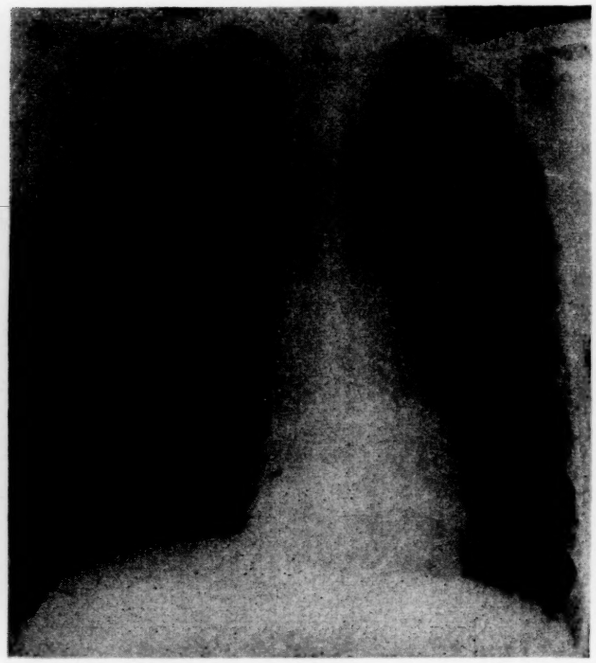


FIG. 2A. Preoperative inspiratory film of patient 6 (E. N.). The mediastinum is pulled into the left chest.

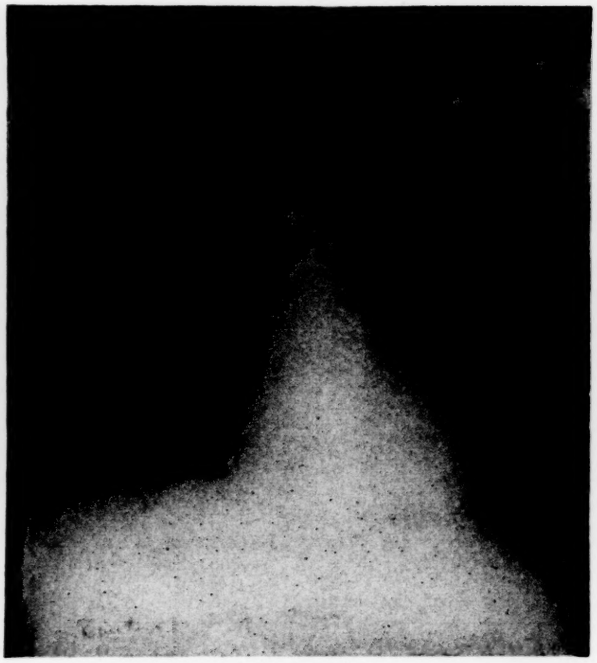


FIG. 2B. Preoperative expiratory film of patient 6 (E. N.) The mediastinum is midline.

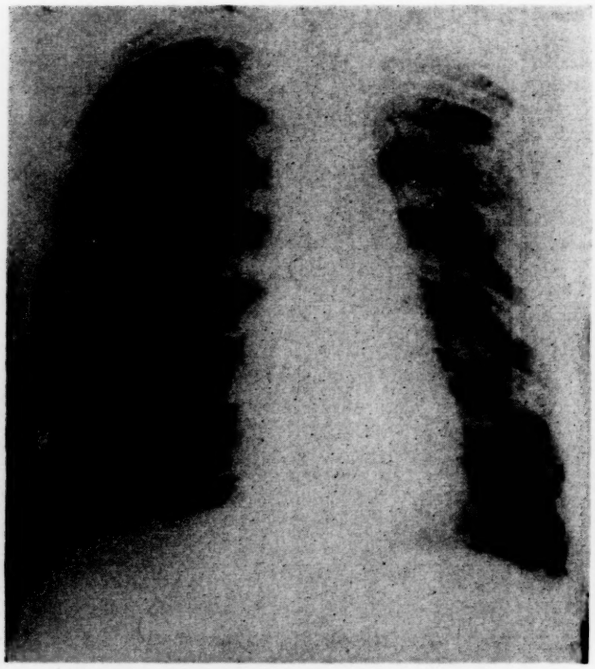


FIG. 2C. Postoperative inspiratory film of patient 6 (E. N.). The mediastinum is midline.

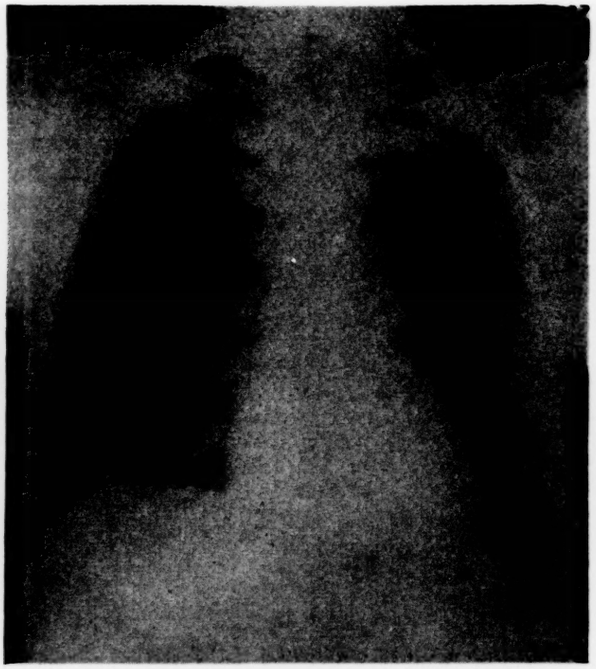


FIG. 2D. Postoperative expiratory film of patient 6 (E. N.). The mediastinum is midline.

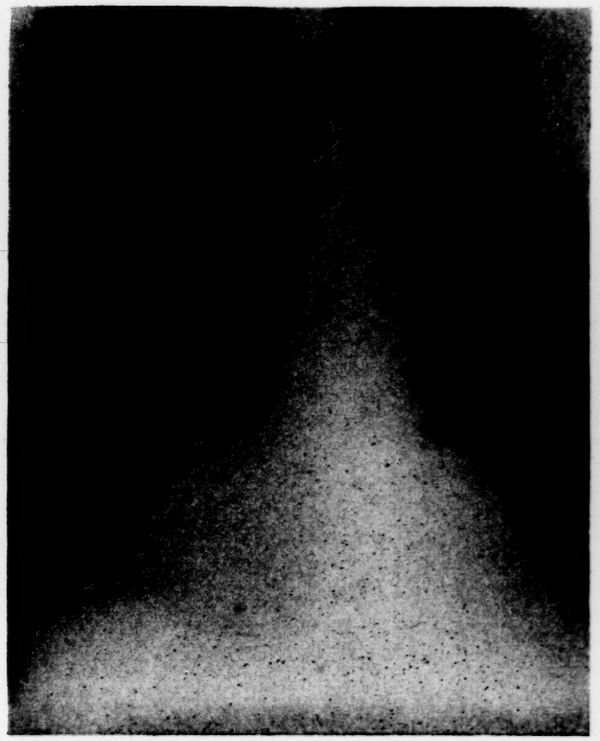


FIG. 3A. Inspiratory film of patient 17 (F. T.). The mediastinum is pulled into the left chest.

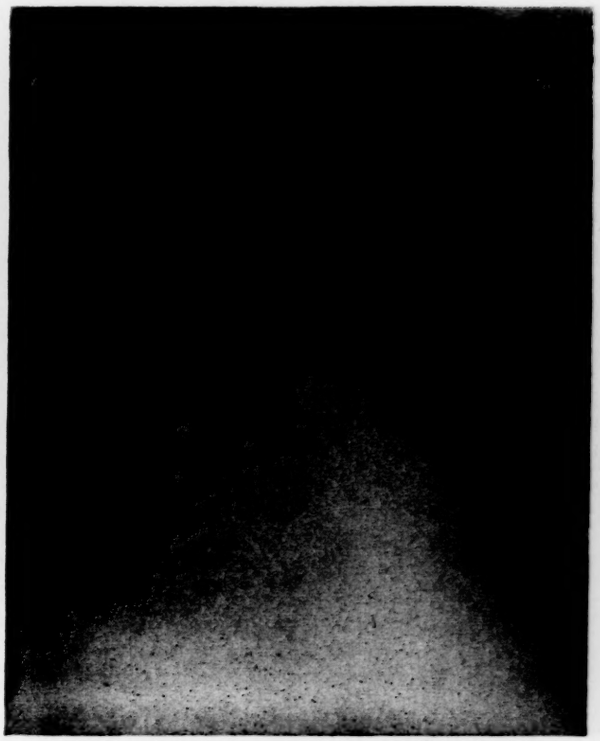


FIG. 3B. Expiratory film of patient 17 (F. T.). The mediastinum is pushed into the right hemithorax.

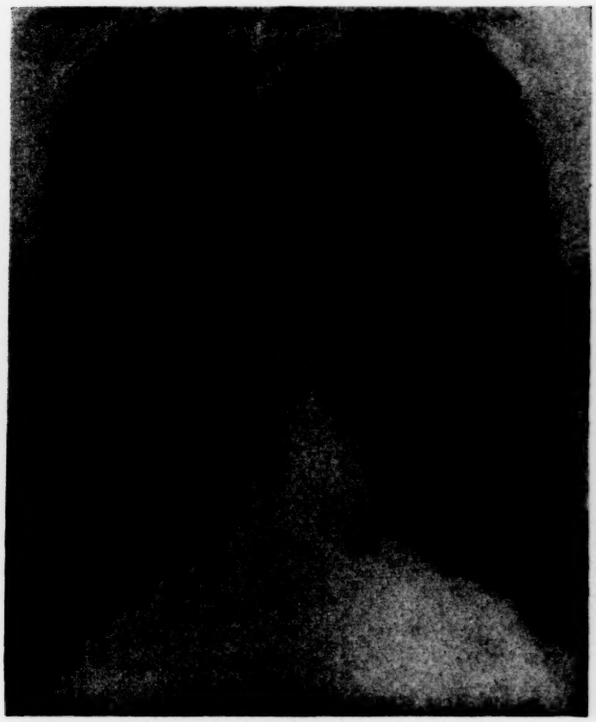


FIG. 4A. Preoperative inspiratory film of patient 19 (G. G.). The mediastinum is in a midline position.

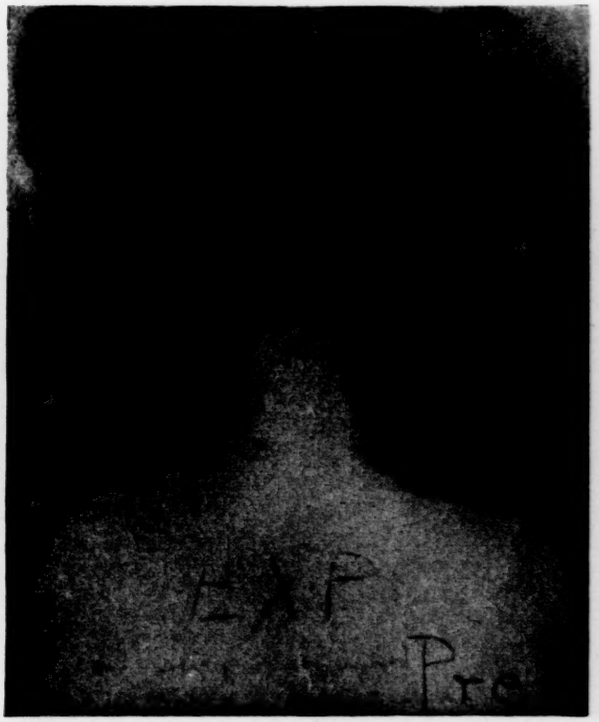


FIG. 4B. Preoperative expiratory film of patient 19 (G. G.) The mediastinum is displaced into the right hemithorax.

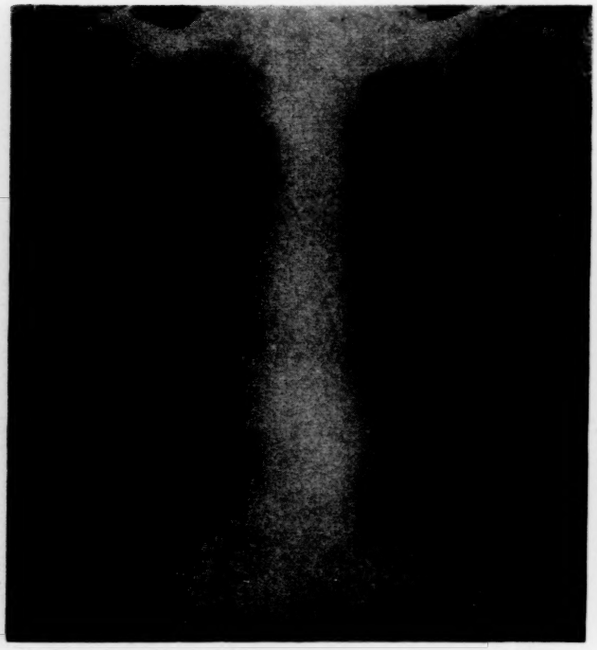


FIG. 4C. Postoperative inspiratory film of patient 19 (G. G.). The mediastinum is midline.

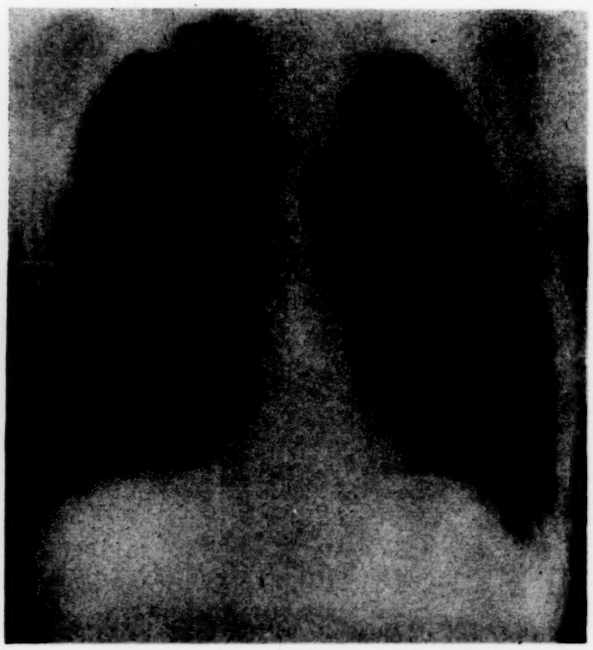


FIG. 4D. Postoperative expiratory film of patient 19 (G. G.). The mediastinum is still midline.

FIG. 5A. Inspiratory film of patient 20 (E. T.). The mediastinum is midline.

FIG. 5B. Expiratory film of patient 20 (E. T.). The mediastinum is pushed into the left hemithorax.

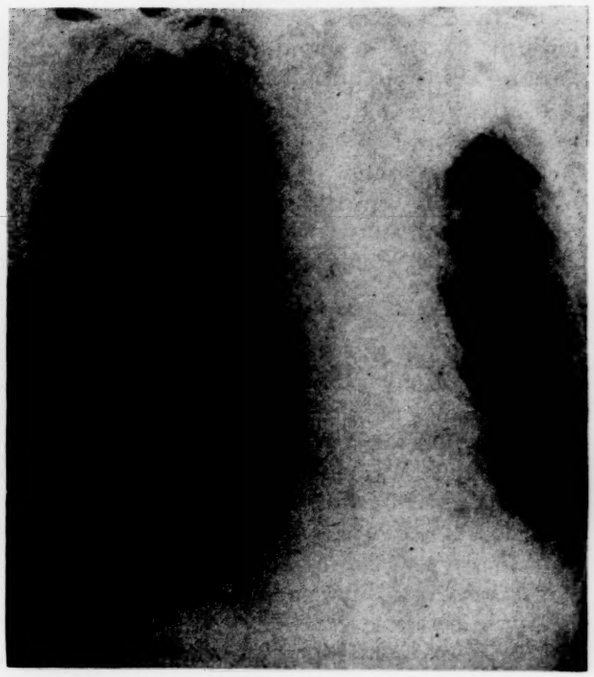


FIG. 6A. Inspiratory film of patient 21 (J. P.). The mediastinum is markedly displaced into the left chest.

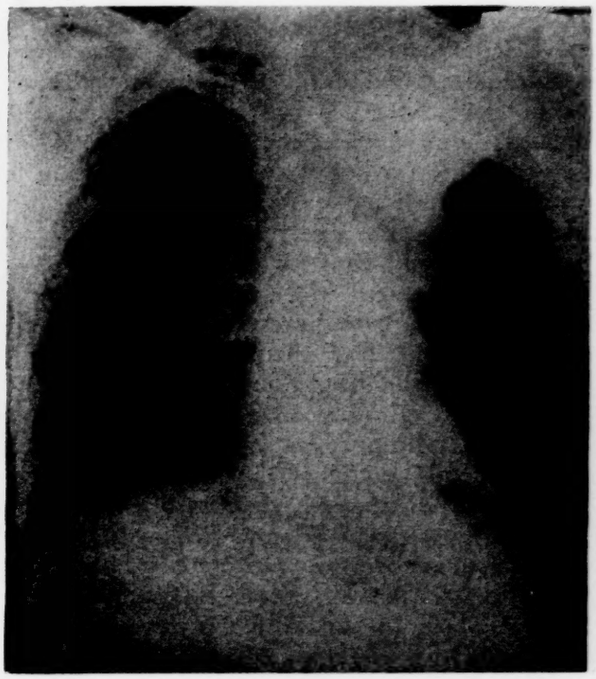


FIG. 6B. Expiratory film of patient 21 (J. P.). The mediastinum is minimally pulled into the left hemithorax.

eased chest during both phases of the respiratory cycle, more on inspiration than on expiration.

Schinz[1] has described three groups of endobronchial stenosis and resultant mediastinal shift. In the first group, pure inspiratory stenosis, the mediastinal movements correspond to stage 1 of Westermark. In the second group, mixed bronchial stenosis, there is obstruction to both inspiration and expiration and the mediastinal shift is therefore as described for stage 2 of Westermark. In the third group, pure expiratory valve-like obstruction, the mediastinal movements correspond to stage 3 of Westermark. Endobrochial obstruction is incomplete in all three types described by Schinz.

It is difficult to understand how stenosis of a large bronchus could be responsible for the inspiratory mediastinal shift described in stage 1 or 2 by Westermark or the first and second groups of Schinz. It is well known that the bronchial tree increases in size during inspiration and decreases in size during expiration.[8] If this thesis is accepted, incomplete endobronchial stenosis could lead only to displacement of the mediastinum to the uninvolved side in expiration, except theoretically in the first few breaths after establishment of the stenosis. The cause for mediastinal displacement toward the involved side in inspiration must be sought elsewhere. Actually, Schinz has recognized that endobronchial stenosis is only one of the many causes of respiratory mediastinal shift. Such movements may occur in pneumothorax, bullous emphysema, paralyzed diaphragm, pleural effusion and pleural thickening. In each instance the cause of the mediastinal movement is the development of differential pressures in the two hemithoraces

TABLE II
BRONCHOSPIROMETRY STUDIES

Case No. and Subject	Partition of Function Between the Two Lungs, %		
	Vital Capacity	Oxygen Uptake	Ventilation
3, J. T., right lung	60	72	67
left lung	40	28	33
6, E. N. right lung	57	53	50
left lung	43	47	50
7, S. L., right lung	60	60	60
left lung	40	40	40
9, J. I., right lung	40	32	35
left lung	60	68	65

during respiration. Recent physiologic studies[9,10] have demonstrated that pulmonary disease may result in decreased pulmonary compliance. That is, pressure difference between the pleura and mouth required to effect a given increase of lung volume (at zero flow) with inspiration is increased. To effect a similar increase in lung volume on each side, unequal intrapleural pressures would thus be required in the two halves of the chest. More negative intrapleural pressure would be required on the diseased side on inspiration. The mediastinum would shift to this side with inspiration and return to the midline on expiration. Complete obstruction of some small bronchioles in the diseased area in one lung is another possible cause for inspiratory mediastinal shift to the diseased side. Medlar[11] has described such findings in tuberculous lesions. In either case, increased resistance to pulmonary deformation of the diseased side is responsible for the mediastinal inspiratory shift.

In the first sixteen cases described in this paper, bronchoscopy was performed in ten instances. In seven, stenosis of a large bronchus was not seen. It is therefore most probable that parenchymal disease and obstruction of small bronchioles or both is the mechanism responsible for mediastinal shift to the diseased side on inspiration in groups I, II and III. The pre- and postoperative findings in patient E. N. are best explained by the latter thesis. The expiratory shift to the contralateral hemithorax in groups III and IV is secondary to incomplete endobronchial obstruction and consequent air trapping. With complete endobronchial stenosis, the mediastinum is pulled into the diseased side during both phases of respiration, more on inspiration than on expiration.

The three patients comprising Group I, those shown to have mediastinal shift on fluoroscopy but not on x-ray, are of considerable interest. These observations demonstrate that fluoroscopy is superior to radiography in the visualization of respiratory mediastinal shift. The recent development of "image amplifiers" for the fluoroscope offers interesting potentialities for the permanent recording of the respiratory mediastinal pendular motion employing a motion picture camera.

Simultaneous bilateral pneumotachygraphic curves through the bronchospirometry tube might have revealed more definite differences between the two lungs in patients with mediastinal respiratory shift but the necessary equipment was not available.

One further point deserves comment. Recent studies[9,10] of the mechanics of pulmonary ventilation have employed intraesophageal pressure as a measure of intrapleural pressure. Since the latter cannot be the same in both pleural cavities in patients with respiratory mediastinal shift, the question arises as to which if either intrapleural pressure is measured in such subjects by means of the intraesophageal pressure.

SUMMARY

1. Five types of mediastinal respiratory shift have been observed in twenty-one patients.

2. In Types I and II the mediastinum is midline on expiration but is displaced to one side during inspiration. In Type II these findings are noted both on fluoroscopy and on x-ray; in Type I the shift is usually not seen on x-ray.

3. In Type III the mediastinum is displaced to one side on expiration and to the opposite side during inspiration.

4. In Type IV the mediastinum is midline on inspiration but is displaced toward the normal side on expiration.

5. In Type V the mediastinum is pulled into the diseased side during both phases of respiration as a result of complete endobronchial occlusion.

REFERENCES

1. Schinz, H. R., Baensch, W. E., Friedl, E. and Vehlinger, E. Roentgen-Diagnostics. Thorax, vol. 3. New York, 1953. Grune & Stratton.
2. Rabin, C. E. X-Ray Diagnosis of Chest Disease. Baltimore, 1952. Williams & Wilkins Co.
3. Shanks, S. C. and Kerley, P. A Text-Book of X-Ray Diagnosis. Chest, vol. 2. Philadelphia, 1951. W. B. Saunders Co.
4. Rigler, L. G. The Chest. Chicago, 1954. The Year Book Publishers, Inc.
5. Westermark, N. Roentgen Studies of the Lungs and Heart. Minneapolis, 1948. The University of Minnesota Press.
6. Golden, R. Abnormally wide respiratory movement of lower lung structures. *Am. J. Roentgenol.*, 44: 325, 1940.
7. Carlens, E. A new flexible double lumen catheter for bronchospirometry. *J. Thoracic Surg.*, 18: 742, 1949.
8. Di Rienzo, S. Radiologic Exploration of the Bronchus. Springfield, Ill. 1949. Charles C Thomas.
9. Lindgren, I., Mead, J., Gaensler, E. A. and Whittenberger, J. L. Pulmonary mechanics in emphysema. Proceedings National Meeting American Federation for Clinical Research, 1953.
10. Stead, W. W., Fry, D. L. and Ebert, R. V. The elastic properties of the lung in normal men and in patients with chronic pulmonary emphysema. *J. Lab. & Clin. Med.*, 40: 674, 1952.
11. Medlar, E. M. The behavior of pulmonary tuberculosis lesions. *Am. Rev. Tuberc.*, 71: 244, 1955.

Congenital Heart Block*

EPHRAIM DONOSO, M.D., EUGENE BRAUNWALD, M.D., SIDNEY JICK, M.D.
and ARTHUR GRISHMAN, M.D.
New York, New York

CONGENTIAL atrioventricular block was first recognized by Morquio[1] in 1901. In recent years an increasing number of cases has been reported. Its incidence among cases of complete heart block has been established by several studies[2–7] which have reported that 8 to 36 per cent of cases of complete atrioventricular block are of congenital origin.

The criteria for the diagnosis of congenital heart block were established by Yater.[8] These are: (1) atrioventricular block proved by graphic methods in a young person; (2) bradycardia noted at an early age; (3) absence of history of infectious disease such as diphtheria, rheumatism or syphilis, which may be responsible for postnatal heart block; (4) the presence of congenital heart disease and/or syncopal attacks during childhood. It has since been observed that typhoid fever, pneumonia, scarlet fever, typhus and rubella also may produce heart block.[9]

The purpose of this paper is to present our studies of eight patients with congenital heart block, including a postmortem examination in one. None of these patients had a history of any of the infectious diseases cited which could be responsible for the heart block.

CASE REPORTS

CASE I. The mother of this patient (H. D., male), during an otherwise uneventful pregnancy, was told that the fetal heart rate was 60 to 70 per minute. Delivery was normal and the patient weighed 6½ pounds at birth. An electrocardiogram taken on the day of birth revealed complete heart block. Cyanosis was first noted at the age of two months. The patient was admitted to the hospital at the age of three and one-half months for a hacking cough and episodes consisting of sudden stiffening of the legs and arms. On physical examination cyanosis and tachypnea were noted. The pulse rate was 60 per minute. A grade 2 systolic murmur was heard at the apex, transmitted to the axilla. P_2 was louder than A_2. The liver was palpable 3 cm. below the costal margin. Fluoroscopy showed right ventricular enlargement. The electrocardiogram revealed complete atrioventricular block with an atrial rate of 125 per minute and a ventricular rate of 60. The QRS complex was supraventricular in form and suggestive of right ventricular hypertrophy. The patient showed no improvement in spite of antibiotic and digitalis therapy. Preterminally bilateral pulmonary rales, peripheral edema and frequent ventricular premature contractions developed. The patient died on May 21, 1953, at the age of five months.

Pathologic report revealed that the heart was considerably enlarged (Figs. 1 and 2) weighing 58 gm. (normal for this age 31 gm.) The aorta lay anterior to the main pulmonary trunk but was not dextroposed. The venae cavae were normal and emptied into a dilated and hypertrophied right atrium. The foramen ovale was patent, the opening measuring 0.5 cm. in diameter. The tricuspid valve was normal. The right ventricle was dilated and hypertrophy noted, measuring 1.0 cm. in thickness. The pulmonary artery arose from the right ventricle. Just below and anterior to the pulmonary ostium there was an interventricular septal defect, measuring 0.6 cm. in diameter. Its upper border consisted of membranous septum; the remainder was surrounded by muscle. The left atrium, which received the pulmonary veins, was thick walled and diminished in size. There was complete atresia of the mitral orifice. The left ventricle was a diminutive chamber. (Figs. 1 and 2.)

CASE II. Patient J. S., male, had been cyanotic with mild exertional dyspnea since infancy. The dyspnea increased at the age of thirty-five years, at which time angiocardiography revealed right ventricular enlargement and pulmonic valvular stenosis with poststenotic dilatation. In 1952 a pulmonary valvulotomy was performed at another hospital, following which the cyanosis disappeared and the dyspnea improved temporarily.

Physical examination, in 1954, at the age of forty years, revealed a pulse rate of 40 per minute and a blood pressure of 145/75. A systolic thrill, grade 4 harsh systolic murmur and grade 2 blowing diastolic murmur were most prominent along the left sternal border at the third intercostal space. Atrial sounds were audible. Roentgenologic examination revealed

* From the Department of Medicine, and the Cardiographic Department, The Mount Sinai Hospital, New York, N. Y.

FIG. 1. Case I. View showing greatly hypertrophied and dilated right ventricle. Pulmonary artery is seen arising from the right ventricle. Arrow points to interventricular septal defect.

FIG. 2. Case I. View showing diminutive left ventricle. Interventricular septal defect is located just beneath aortic valve and presumably directed blood from right ventricle to aorta.

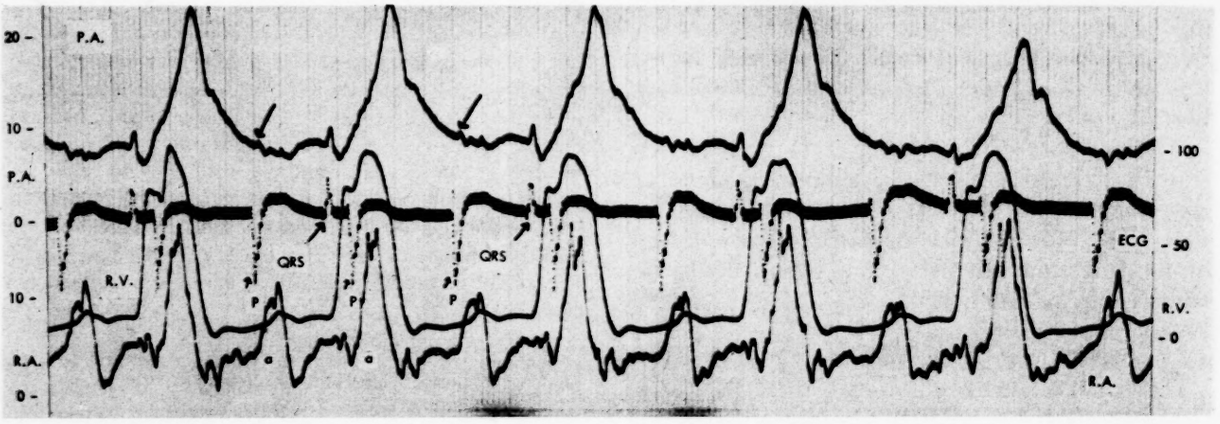


FIG. 3. Simultaneous pulmonary artery (P.A.), right ventricular (R.V.) and right atrial (R.A.) pressure pulses with endocardial (right atrial) electrocardiographic lead in Case II (patient J. S.).

hypertrophy of the right ventricle. Electrocardiogram showed complete atrioventricular block. The QRS complex was of the supraventricular type. Right axis deviation was present but there was no evidence of right ventricular hypertrophy. Cardiac catheterization (Figs. 3 and 4) revealed: (1) evidence of pulmonic stenosis with a right ventricular pressure of 96/5 mm. Hg and a pulmonary artery pressure of 27/12 mm. Hg; (2) evidence of an interventricular septal defect with a left-to-right shunt as indicated by an increment of 2.8 volumes per cent in the oxygen content of right ventricular as compared with right atrial blood specimens; (3) brachial arterial pressure of 93/38 mm. Hg; (4) peripheral arterial oxygen saturation of 94 per cent. The clinical and catheterization findings suggest a diagnosis of pulmonic stenosis with interventricular septal defect and complete congenital heart block, but tetralogy of Fallot cannot be ruled out.

CASE III. Patient I. I., female, was known to have had a heart murmur since childhood, but was essen-

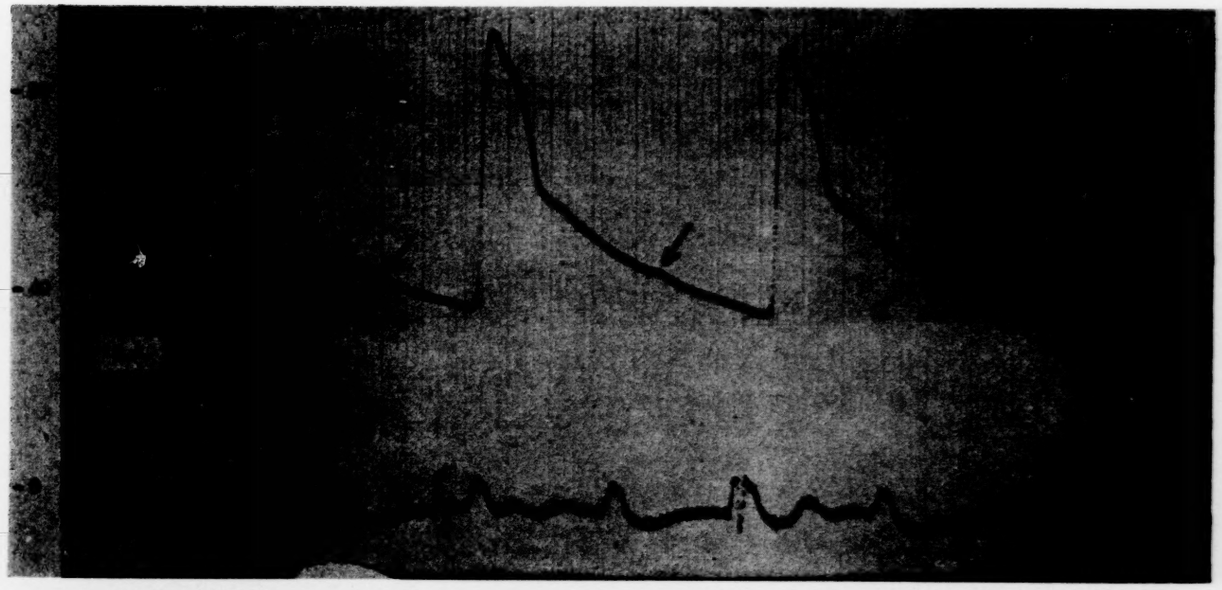


FIG. 4. Direct brachial artery (B.A.) pressure in Case II (patient J. S.). Arrows indicate alterations in B.A. contour produced by atrial contraction.

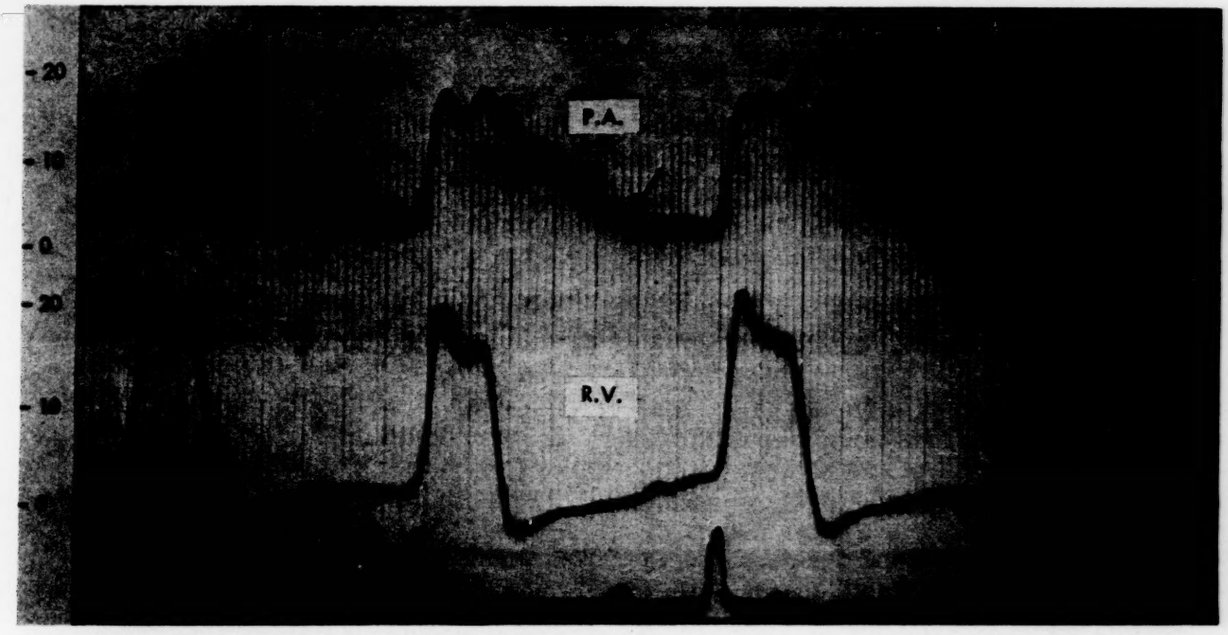


FIG. 5. Simultaneous pulmonary artery (P.A.) and right ventricular (R.V.) pressures in Case III (patient I. I.). Arrows indicate alterations in contour of P.A. tracing produced by atrial contraction. Note that effect of atrial contraction begins earlier in the P.A. as compared with the R.V. tracing

tially asymptomatic. Physical examination in 1954, at the age of thirty-four years, revealed a pulse rate of 44 per minute. A blowing, grade 1, systolic murmur was heard at the apex, with audible atrial sounds. Roentgenologic examination of the heart and lungs revealed no abnormality. Electrocardiogram showed complete atrioventricular block. The QRS complex was supraventricular in form and was normal. Cardiac catheterization in 1954 revealed normal pressures in the pulmonary artery, right ventricle and right atrium. (Fig. 5.) While there was no clear-cut evidence of an intracardiac shunt, the oxygen content of blood samples from the right ventricle and pulmonary artery averaged 0.8 volumes per cent greater than that of samples from the right atrium. Clinical diagnosis was complete congenital heart block without underlying

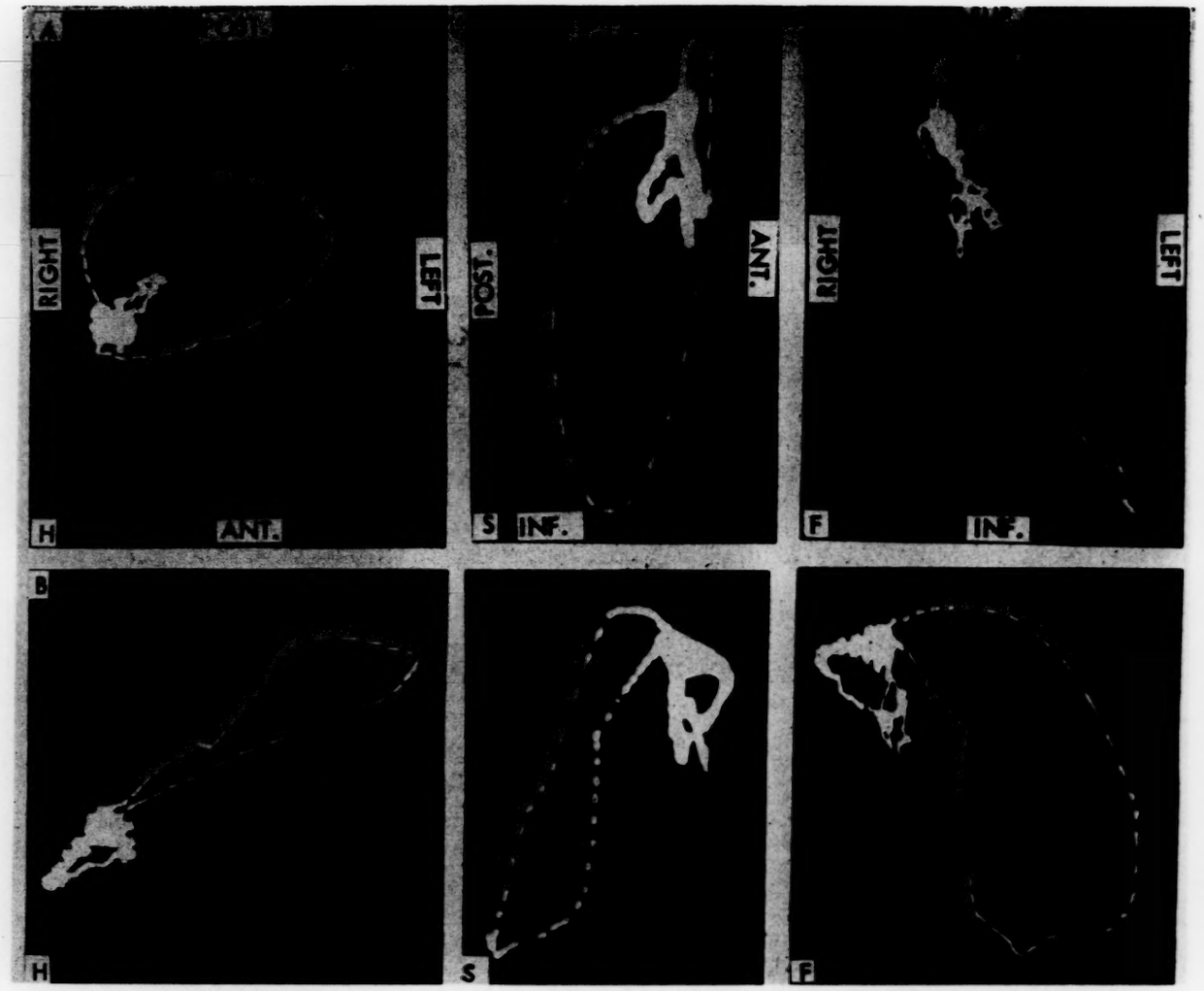


FIG. 6. Spatial vectorcardiograms (cube reference system) in Case VI (patient I. A.) taken while QRS was supraventricular (above) and idioventricular in form (below). H = horizontal plane; S = sagittal plane; F = frontal plane.

heart disease, although an interventricular septal defect has not been ruled out completely.

CASE IV. Patient F. B., female, had a history of a heart murmur since infancy but was asymptomatic. Physical examination at the age of sixteen years revealed a pulse rate of 50 per minute, a systolic thrill and a grade 3 harsh systolic murmur along the left sternal border in the third intercostal space. Fluoroscopy showed the heart to be enlarged, with dilatation of the right pulmonary artery. Angiocardiography was typical of infundibular pulmonic stenosis and demonstrated hypertrophy and dilatation of the right ventricle, a deformed and stenotic pulmonary conus, and aneurysmal dilatation of the pulmonary artery. Electrocardiogram revealed complete atrioventricular block with supraventricular complexes. Clinical diagnosis was congenital infundibular pulmonary stenosis and complete congenital heart block.

CASE V. Patient M. M., female, had always been asymptomatic. Physical examination at the age of thirty years revealed a bradycardia of 40 per minute. There was a grade 2 systolic murmur which was loudest at the fourth intercostal space at the left sternal border. Roentgenologic examination of the heart was suggestive of left ventricular enlargement. Electrocardiogram showed complete atrioventricular block. The QRS complex was supraventricular in form and was normal. Clinical diagnosis was probable interventricular septal defect and complete congenital heart block.

CASE VI. Patient F. A., male, was known to have had a heart murmur since the age of four years. Examination at the age of six years, in 1952, showed a pulse rate of 50 per minute. A grade 3, harsh, systolic murmur was heard most prominently in the fourth intercostal space along the left sternal border.

The remainder of the physical examination was normal. Fluoroscopic and roentgenologic examinations showed a normal cardiac silhouette. Electrocardiograms revealed complete atrioventricular block. The QRS has varied on different occasions between a normal supraventricular and an idioventricular complex. (Fig. 6.) The patient has been followed up for four years and has remained asymptomatic. Clinical diagnosis was interventricular septal defect, with complete congenital heart block.

CASE VII. Patient, M. T., a twenty-eight year old Navy nurse, has always been asymptomatic. Physical examination revealed a pulse rate of 40 per minute. A grade 1 short blowing systolic murmur was heard at the apex. The remainder of the physical examination was normal. Roentgenologic and fluoroscopic examinations showed a normal cardiac silhouette. Electrocardiogram revealed complete atrioventricular block and normal supraventricular complexes. Clinical diagnosis was complete congenital heart block without underlying heart disease.

CASE VIII. Patient B. R., female, was known to have had heart block and a heart murmur since the age of eight years. An electrocardiogram taken at that time revealed complete atrioventricular block with the QRS complex supraventricular in form. Physical examination, in 1936, when the patient was twenty-six years old, revealed a loud, blowing systolic murmur over the apex and mid-sternal region. A loud, blowing diastolic murmur was heard at the base. The remainder of the physical examination was normal. Fluoroscopic examination revealed a cardiac silhouette which was enlarged both to the right and left. Congestive failure developed which responded poorly to treatment. The patient died at the age of twenty-nine. Permission for postmortem examination was not granted. Clinical diagnosis was congenital heart disease of undetermined type with complete congenital heart block.

DISCUSSION

Pathologically, congenital atrioventricular block does not usually occur as an isolated finding but is frequently associated with anatomic cardiac anomalies of congenital origin. Table 1 lists seventeen published cases of congenital heart block in which postmortem examination has been performed[8,10–24] (including Case 1 of this report) and demonstrates the considerable variation in the associated cardiac malformations. Twelve of these seventeen cases had an interventricular septal defect with or without other cardiac anomalies, in five cases the interventricular septum was intact. Although the association of congenital heart block with interventricular septal defect is well recognized, it should be noted that in the 200 cases of interventricular septal defect reviewed by Brown[25] no cases of congenital heart block were found. Six of the seventeen patients upon whom autopsy was performed had a patent ductus arteriosus, and four had coarctation of the aorta as part of the cardiac anomalies. Case 1 of our series represents the first reported case of mitral atresia associated with congenital heart block.

It appears that there is a group of patients with congenital heart block who show no clinical evidence of associated heart disease. Although this has not been confirmed by postmortem study, Zimmerman et al.[26] found no abnormalities at cardiac catheterization performed twice on a patient with congenital heart block. Cases III and VII of this series probably also belong to this group.

Seven cases of congenital atrioventricular block have been reported in which adequate histologic studies of the heart were performed.[8,10,13,14,17,19,20] The central fibrous body appeared to separate the atrioventricular node from the rest of the conducting system in four cases. In the other three cases the bundle of His was virtually absent; it appeared "punched out" by an interventricular septal defect in one case, rudimentary in another, and could not be identified in the third.

Mitral Atresia. Case 1 is of particular interest because of the rare occurrence of congenital mitral atresia. Thirty-eight cases of this malformation have been published prior to this report.[27–30] The usual anatomic findings in this condition are enlargement of the right atrium and ventricle associated with a small left atrium and diminutive left ventricle. A left-to-right shunt generally takes place through an interatrial communication, rarely through a connecting venous anomaly. Interventricular septal defect and transposition of the great vessels are frequent concomitant anomalies. In the case reported here an interatrial communication shunted the entire pulmonary venous return into the right atrium, while blood passed into the aorta from the right ventricle through an interventricular septal defect. The prognosis in this condition is grave, with death usually occurring in infancy.[25]

Electrocardiogram. The ventricular rate in congenital heart block is usually more rapid than in acquired block. In congenital block the ventricular rate ranges between 40 and 80 beats per minute,[4,20,31–33] the more rapid rates occurring in infancy and early childhood. This is in

TABLE I
POSTMORTEM FINDINGS IN CONGENITAL HEART BLOCK

Author	Sex and Age at Death	Interventricular Septal Defect	Patent Ductus Arteriosus	Coarctation of the Aorta	Other Major Anomalies
Wilson, Grant[10]*	F, 14 mo.	+	+	−	Atresia of root of pulmonary artery
Perotti[11]	F, 3 days	+	−	−	
Yater[5]	M, 2 wk.	+	+	−	Transposition of great vessels; interatrial communication
Abbott, Moffatt[12]	M, 20 yr.	+	+	−	Transposition of great vessels; cor biatriatum triloculare; double mitral ostium; right conus stenosis; pulmonary arteriovenous aneurysm
Yater et al.[13]	M, 2 mo.	+	−	−	
Yater et al.[14]	M, 18 hr.	+	−	−	
Witt[15]	M, 2½ mo.	−	−	+	Patent foramen ovale
Abbott[16]	F, 8½ mo.	−	−	+	Corrected transposition of great vessels; anomalous insertion of anterior mitral segment
Wallgren, Winblad[17]	F, 2½ mo.	−	−	−	Persistent ostium primum
Hoekenga[18]	F, 4 mo.	+	+	−	Cor biatrium triloculare; patent foramen ovale; pulmonic atresia
Wendkos, Study[19]	M, 3 days	−	+	+	
Turpin et al.[20]	M, 6½ mo.	+	−	−	Rudimentary left ventricle; hypertrophy of right ventricle; anomaly of posterior leaflet of mitral valve
Dickson, Jones[21]	M, 2 mo.	+	+	+	Transposition of great vessels; interatrial septal defect; left ventricular hypertrophy
Stadler et al.[22]	?, 3½ mo.	−	−	−	Endocardial fibroelastosis
Berneiter[23]*	F, 14 mo.	+	−	−	Tetralogy of Fallot
Aitchison et al.[24]	M, 34 yr.	+	−	−	Patent foramen ovale; transposition of great vessels (Spitzer's type IV)
Donoso et al.	M, 5 mo.	+	−	−	Atresia of mitral orifice; diminutive left ventricle; patent foramen ovale

* Incomplete heart block.

contrast to the finding that the ventricular rate is usually less than 50 per minute in acquired heart block.

The QRS complex in congenital heart block is generally supraventricular in form.[6] In this series seven of the eight electrocardiograms revealed QRS complexes of the supraventricular type. In the remaining patient (Case VI) both supraventricular and idioventricular types of complexes were present intermittently. Vectorcardiograms of both of these types of complexes are demonstrated in Figure 6. In acquired heart block more than half of the cases show idioventricular QRS complexes.[6] Slower ventricular rates usually occur when the pacemaker is idioventricular than when it originates in the atrioventricular node or bundle of His. This difference in rate was observed in Case VI in whom periods of idioventricular and supraventricular complexes alternated. The more rapid ventricular rates reported in congenital heart block are probably related to the more frequent occurrence of supraventricular complexes and the younger age of this group as contrasted with patients with acquired heart block. The virtually normal ventricular rate in some patients with congenital heart block may be responsible for the cases which are overlooked for many years. Congenital atrioventricular block may be suspected in utero when a relatively slow fetal heart rate is present,[34,35] as in Case I.

The varying P-P interval in complete heart block is a well known phenomenon.[36–37] P-P intervals separated by a QRS complex are usually shortened (positive chronotropic effect) but may occasionally be prolonged (negative chronotropic effect) when compared to P-P intervals without an interposed QRS complex. Seven of the eight cases in this series revealed a positive chronotropic effect, indicating that there appears to be no significant difference between congenital and acquired heart block in this respect.

In the case of congenital heart block reported by Wilson and Grant[10] it was noted that although the interventricular septum was absent, the ventricular complex of the electrocardiogram started with a Q wave. No satisfactory explanation was offered. In Cases III and V, in which the clinical diagnosis is interventricular septal defect, the initial deflection of the vectorcardiogram is directed anteriorly, superiorly and to the right, as in the normal.[38] This initial deflection is generally considered to represent the balance of forces generated at the time of septal depolarization. Whether or not the interventricular septum is intact in these cases, the impulse apparently begins in the atrioventricular bundle and the initial wave of depolarization proceeds in the usual direction. Since the atrioventricular bundle in cases of interventricular septal defect is usually located either on the upper border of the interventricular septum or on the surface of a muscular prominence on the posterior wall of the left ventricle,[39] it is to be expected that the "septal vector" would be directed in the usual manner.

Hemodynamics. Cardiac catheterization was performed in Cases II and III, providing the opportunity for studying the hemodynamics of complete heart block. The first such observations in atrioventricular block were reported by Richards et al.[40,41] who studied patients with acquired heart block. The hemodynamics in congenital heart block are fundamentally the same as in acquired block but are modified by the associated cardiac anomalies.

Examination of the right atrial pressure pulse in Case II (Fig. 3) reveals atrial contraction ("a") waves of varying amplitude. When atrial contraction takes place during ventricular systole, the "a" waves are of high amplitude, reaching a peak of 15 mm. Hg. However, these waves are considerably smaller, reaching a peak of only 8 mm. Hg, when atrial contraction takes place during ventricular diastole, as is normally the case. This difference in amplitude can be explained by two factors. During ventricular systole the atrium contracts against a closed tricuspid valve. This reduces the volume of the chamber in which right atrial contraction takes place and results in a greater pressure rise than when atrial systole takes place with an open tricuspid valve. In addition, it appears that the atrial end-diastolic pressure is higher preceding the larger "a" waves. This higher end-diastolic pressure may reflect a greater end-diastolic atrial volume and may result in more vigorous atrial contraction. (Figs. 3 to 5.)

The pulmonary artery, right ventricle and brachial artery pressure pulses (Figs. 3 to 5) during diastole are altered by the simultaneous occurrence of atrial contraction. Harvey et al.[42] and McCord and Blount[43] have observed a similar phenomenon in pulmonary artery pressure tracings of patients with atrial flutter, while Howarth[44] has noted atrial contraction

waves in the systemic arterial pulse in a variety of conditions. Such waves have not, however, been previously reported in the pulmonary arterial pressure pulse in heart block. These waves may result from an external impact on the pulmonary artery or aorta produced by the contracting atrium or by the forward transmission of the atrial contraction wave through the ventricle and the closed semilunar valves. We favor the former possibility, particularly in regard to the pulmonary artery waves. It has been reported that in dogs the atrial contraction wave normally is delayed as it is transmitted from right atrium to right ventricle.[45] That this also occurs in man is evident in Figure 3. Examination of the pressure tracings (Figs. 3 and 5) reveals that the atrial contraction waves occur virtually synchronously in the pulmonary artery and right atrium but later in the right ventricle. Were the atrial contraction wave transmitted through the right ventricle and closed semilunar valves, it would not be seen earlier in the pulmonary artery than in the right ventricle. Furthermore, the contour of the waves in the pulmonary artery which are associated with atrial contraction are irregular in appearance, as might be expected from the vibrations produced by an external impact. The left atrium is in anatomic proximity to the aorta and pulmonary artery and its contractions may well be transmitted directly to these vessels.

Prognosis. The prognosis in congenital heart block is dependent primarily on the nature of any cardiac malformation which may coexist. Campbell[46] observed seven adult patients with congenital heart block for nine years during which period they exhibited virtually no cardiac symptoms. Turner[47] has reported a case of congenital heart block in a twenty-four-year old pilot who was asymptomatic. It is also the prevailing opinion that when congenital heart block exists in a pregnant patient, the course of pregnancy will be uneventful and the patient should be permitted to proceed to term in the usual manner, unless associated heart disease is present.[26,48–51] In congenital heart block without associated heart disease it is not necessary to restrict normal activity, and this condition is compatible with survival to old age.

SUMMARY

1. Studies of eight cases of congenital heart block, including the first published case of mitral atresia with congenital heart block, are presented.

2. Review of the literature revealed that of the seventeen cases of congenital heart block reported with postmortem findings interventricular septal defect, with or without other anomalies, was the most common associated congenital lesion, being present in twelve cases, while patent ductus arteriosus was found in six and coarctation of the aorta in four cases as part of the malformation. Congenital heart block may occur in patients who show no clinical evidence of associated heart disease.

3. The diagnostic value of the electrocardiogram in differentiating congenital from acquired heart block is stressed. The ventricular rate in congenital heart block is generally 40 to 80 beats per minute and the QRS complex is usually supraventricular in form. This is in contrast to the somewhat slower ventricular rate and idioventricular form of the QRS complex usually found in acquired heart block.

4. Cardiac catheterization in two of our patients revealed that (a) when atrial contraction occurs during ventricular systole, the "a" waves were considerably higher than those recorded when atrial contraction occurs during ventricular diastole; (b) direct pulmonary artery, right ventricular and brachial artery pressures revealed the influence of the atrial contractions. The possible mechanisms of the hemodynamic observations are discussed.

5. The prognosis of congenital heart block is primarily that of the associated heart disease, when present.

Acknowledgment: We are indebted to Dr. A. J. Gordon for permission to utilize the pressure records, to the Dept. of Pathology for permission to publish the postmortem findings in Case I, and to Dr. I. R. Roth who permitted the study of Case VIII.

REFERENCES

1. Morquio, L. Sur une maladie infantile et familiale caractérisée par des modifications permanentes du pouls, des attaques syncopales et épileptiformes. *Arch. de méd. d. enf.*, 4: 467, 1901.
2. Ellis, L. B. Studies in complete heart block. I. A clinical analysis of 43 cases. *Am. J. M. Sc.*, 183: 225, 1932.
3. Graybiel, A. and White, P. D. Complete auriculoventricular dissociation; a clinical study of 72 cases with a note on a curious form of auricular arrhythmia frequently observed. *Am. J. M. Sc.*, 192: 334, 1936.
4. Campbell, M. Complete heart block. *Brit. Heart J.*, 6: 69, 1944.

5. Zoubras, J. Les dissociations auriculo-ventriculaires congénitales. Thèse & Lyon, 1944. M. Audin & Cie.
6. Kay, H. B. Ventricular complexes in heart block. *Brit. Heart J.*, 10: 177, 1948.
7. Ide, L. W. The clinical aspects of complete auriculo-ventricular heart block: a clinical analysis of 71 cases. *Ann. Int. Med.*, 32: 510, 1950.
8. Yater, W. M. Congenital heart block, review of literature, report of case with incomplete heterotaxy, electrocardiogram in dextrocardia. *Am. J. Dis. Child.*, 38: 112, 1929.
9. Logue, R. B. and Hanson, J. F. Complete heart block in German measles. *Am. Heart J.*, 30: 205, 1945.
10. Wilson, J. G. and Grant, R. T. Congenital malformation of the heart in an infant associated with partial heart block. *Heart*, 12: 295, 1926.
11. Perotti, D. Blocco cardiaco congenito con vizio di conformazione del cuore. *Boll. Soc. med.-chir., Pavia*, 3: 1, 1928.
12. Abbott, M. E. and Moffatt, D. Cited by Abbott, M. E. In: Nelson Loose Leaf Medicine. Section on congenital heart disease, vol. 4, p. 207. New York, 1932. Thos. Nelson & Sons.
13. Yater, W. M., Lyon, S. A. and McNabb, P. E. Congenital heart block, review and report of the second case of complete block studied by serial sections through the conduction system. *J. A. M. A.*, 100: 1831, 1933.
14. Yater, W. M., Leaman, W. G. and Cornell, V. H. Congenital heart block. Report of a third case of complete heart block studied by serial sections through the conduction system. *J. A. M. A.*, 102: 1660, 1934.
15. Witt, D. B. Congenital complete auriculo-ventricular heart block. *Am. J. Dis. Child.*, 47: 381, 1934.
16. Abbott, M. E. Atlas of congenital cardiac disease, p. 58. Published by the American Heart Association, 1936.
17. Wallgren, A. and Winblad, S. Congenital heart block. *Acta paediat.*, 20: 175, 1937–1938.
18. Hoekenga, M. Complete heart block in an infant associated with multiple congenital cardiac malformations. *Am. J. Dis. Child.*, 69: 231, 1945.
19. Wendkos, A. and Study, R. S. Familial congenital complete A.V. heart block. *Am. Heart J.*, 34: 138, 1947.
20. Turpin, R., Lenègre, J. and Chassagne, P. Étude anatomo-clinique d'un cas de dissociation auriculo-ventriculaire chez un nourrisson de 7 mois. *Arch. Franç. pédiat.*, 4: 617, 1947.
21. Dickson, R. W. and Jones, J. P. Congenital heart block in an infant with associated multiple congenital cardiac malformations. *Am. J. Dis. Child.*, 75: 81, 1948.
22. Stadler, H. E., Reid, C. A. and Friedman, H. P. Prenatal fibroelastosis ("fetal endocarditis") manifested clinically by total heart block. *J. Pediat.*, 36: 370, 1950.
23. Berneiter, M. Congenital heart block. *J. A. M. A.*, 150: 792, 1952.
24. Aitchison, J. D., Duthie, R. J. and Young, J. S. Palpable venous pulsations in a case of transposition of both arterial trunks and complete heart block. *Brit. Heart J.*, 12: 63, 1955.
25. Brown, J. Congenital heart disease. London, 1951. Stapler Press.
26. Zimmerman, H. A., Ryan, J. M. and Linn, R. L. Congenital complete heart block: Results of intracardiac catheterizations during pregnancy. *Am. Pract. & Digest Treat.*, 2: 609, 1951.
27. McIntosh, C. A. Cor biatriatum triloculare. *Am. Heart J.*, 1: 735, 1926.
28. Manhoff, L. J., Jr. and Howe, J. S. Congenital heart disease: tricuspid atresia and mitral atresia associated with transposition of great vessels; report of two cases. *A. Heart J.*, 29: 90, 1945.
29. Edwards, J. E. and DuShane, J. W. Thoracic venous anomalies: I. Vascular connection of the left atrium and the left innominate vein (levo-atriocardinal vein) associated with mitral atresia and premature closure of the foramen ovale. II. Pulmonary veins draining wholly into the ductus venosus. *Arch. Path.*, 49: 517, 1950.
30. Large, H. L., Jr. Congenital mitral atresia. Report of two cases. *Am. J. M. Sc.*, 219: 268, 1950.
31. Leys, D. Congenital heart block. *Brit. Heart J.*, 5: 15, 1943.
32. Taussig, H. B. Congenital malformations of the heart. New York, 1947. The Commonwealth Fund.
33. Burchell, H. B. The electrocardiogram in congenital heart disease. *M. Clin. North America*, 33: 1157, 1949.
34. Geiger, C. J. and Hines, L. E. Prenatal diagnosis of complete congenital heart block. *J. A. M. A.*, 115: 2272, 1940.
35. Riley, I. D. Complete auriculo-ventricular heart block in foetus and newborn. *Arch. Dis. Child.*, 24: 309, 1950.
36. Roth, I. R. and Kisch, B. The mechanism of irregular sinus rhythm in auriculo-ventricular heart block. *Am. Heart J.*, 36: 257, 1948.
37. Rosenbaum, M. B. and Lepeschkin, E. The effect of ventricular systole on auricular rhythm in auriculo-ventricular block. *Circulation*, 11: 240, 1955.
38. Grishman, A. and Scherlis, L. Spatial vectorcardiography. Philadelphia, 1952. W. B. Saunders Company.
39. Keith, A. Malformations of the heart. *Lancet*, 2: 519, 1909.
40. Richards, D. W., Cournand, A., Motley, H. L., Dresdale, D. T. and Ferrer, M. I. Relation between electrical and mechanic events of the cardiac cycle in normal and abnormal clinical states. *Tr. A. Am. Phys.*, 60: 65, 1947.
41. Coblentz, B., Harvey, R. M., Ferrer, M. I., Cournand, A. and Richards, D. W. The relationship between electrical and mechanical events in the cardiac cycle of man. *Brit. Heart J.*, 11: 1, 1949.
42. Harvey, R. M., Cournand, A. and Ferrer, M. I. Cardiocirculatory performance in atrial flutter. *J. Clin. Investigation*, 33: 940, 1954.
43. McCord, M. C. and Blount, S. G. Auricular flutter: hemodynamic and ausculatory findings. *Clin. Research Proc.*, 3: 53, 1955.
44. Howarth, S. Atrial waves on arterial pressure records in normal rhythm, heart block, and auricular flutter. *Brit. Heart J.*, 16: 117, 1954.
45. Little, R. C. Effect of atrial systole on ventricular

pressure and closure of the A-V valves. *Am. J. Physiol.*, 166: 289, 1951.

46. CAMPBELL, M. Congenital complete block. *Brit. Heart J.*, 5: 15, 1943.
47. TURNER, L. B. Asymptomatic congenital heart block in an Army Air Force pilot. *Am. Heart J.*, 34: 426, 1947.
48. BARTON, R. M. and LADUE, C. W. Complete heart block in a case of pregnancy. *Am. J. Med.*, 4: 447, 1948.
49. MOWBRAY, R. and BOWLEY, C. C. Congenital complete heart block complicating pregnancy. (A report of three cases.) *J. Obst & Gynaec. Brit. Emp.*, 55: 438, 1948.
50. FERGUSON, H. and PORTER, C. E. Complete heart block associated with pregnancy. *South. M. J.*, 43: 44, 1950.
51. ZIEGLER, A. M. Pregnancy with complete congenital heart block. *Am. J. Obst & Gynec.*, 62: 445, 1951.

Relationship of Portal Hypertension to Ascites in Laennec's Cirrhosis*

WILLIAM J. EISENMENGER, M.D. *and* WILLIAM F. NICKEL, M.D.
New York, New York

THE complexity of the problem of ascites formation has stimulated endless debate concerning the relative importance of the various factors involved.[1,2] That portal hypertension alone does not usually cause ascites is well known from observations on patients with portal vein thrombosis, most of whom do not have ascites. It is apparent that the hypoalbuminemia of advanced Laennec's cirrhosis is not essential to the development of ascites since in many such cases the intravenous administration of large amounts of serum albumin has no effect whatever on the accumulation of ascites. An increased amount of pituitary antidiuretic hormone may account for the renal retention of water which permits the accumulation of ascites; that this excessive antidiuretic activity is a secondary factor seems probable from the observation that the water retained in the advanced stage of cirrhosis is localized as ascitic fluid and is not retained as generalized edema. Also, the renal retention of sodium, presumably stimulated by the adrenal gland, is only enough to provide sufficient sodium for the ascites retained and to maintain normal levels of sodium in the other body fluids. Thus the abnormal retention of sodium and water by the kidney appears to be secondary rather than primary to the accumulation of ascites.

For many years portal hypertension was considered to play an important role rather than a secondary one in the formation of ascites as a result of increased extravasation of fluid from the portal vascular system. With this in mind, the Eck fistula was devised for the purpose of relieving ascites by reducing portal hypertension in patients with cirrhosis. However, thus far this operation has been little used for this purpose, presumably because, until recently, portacaval anastomosis often could not be tolerated by the patient who had cirrhosis severe enough to cause refractory ascites. Most of these patients did not survive, so that for some years portacaval anastomosis could not be used for studying the effect of portal pressure on ascites formation.

Some further delay in testing this procedure was caused by the current tendency to doubt the importance of portal hypertension in the development of ascites in Laennec's cirrhosis.[1] The reasons for this doubt appear to arise principally from two sets of observations, neither of which, however, is necessarily directly applicable to the problem of Laennec's cirrhosis.

1. Portal hypertension secondary to extrahepatic thrombosis of the portal vein may not be associated with ascites. This is a well documented observation. However, portal hypertension in such a situation involves only the extrahepatic portal vascular system, and the large intrahepatic portal system has normal or reduced pressure. Thus the situation is quite different from that in Laennec's cirrhosis in which portal hypertension extends to the portal area of the hepatic lobule.

2. A second group of observations has to do with the rapid development of ascites in dogs following supradiaphragmatic constriction of the inferior vena cava, despite the lack of significant portal hypertension.[3] This observation is often cited as an argument against the importance of portal hypertension in the development of ascites in Laennec's cirrhosis. However, the added factor of hypertension in the hepatic veins, central veins and sinusoids has been introduced in these experimental animals which is not the usual situation in Laennec's cirrhosis.

Consequently, these two sets of observations which are often cited to cast doubt on the importance of portal hypertension in the development of ascites in Laennec's cirrhosis really are not entirely applicable to the problem.

A more direct method of clarifying the rela-

* From The Rockefeller Institute for Medical Research and the New York Hospital, New York, New York.

tionship between portal hypertension and ascites formation in patients with Laennec's cirrhosis is by use of portacaval anastomosis. Surgical procedures used on patients with advanced cirrhosis have improved greatly in the past ten years so that with carefully selected and well prepared patients one can expect that even patients with chronic maximal ascites can now tolerate the procedure. Accordingly, five patients with Laennec's cirrhosis and chronic ascites were subjected to portacaval anastomoses and in each instance ascites disappeared shortly thereafter. The present report summarizes the effects on the metabolism of salt and water which resulted from a reduction in portal hypertension by means of portacaval anastomosis.

It is strongly emphasized that the purpose of this study is not to advocate portacaval anastomosis as a method of treating chronic ascites but rather to provide information not otherwise available on the relationship between portal hypertension and ascites formation in Laennec's cirrhosis. While occasional cases may occur in which portacaval anastomosis is indicated primarily for the control of ascites, each such case must be considered and prepared with the utmost care.

MATERIALS AND METHODS

Five patients with Laennec's cirrhosis, in whom ascites had been present constantly from one to six years, were selected for portacaval anastomosis. The prolonged periods over which there was no detectable decrease in the tendency to form ascites despite adequate medical therapy gave fair assurance that spontaneous disappearance of ascites would not occur, except possibly in Case v. In three of the patients (M. L., N. D., A. C.) esophageal hemorrhages had occurred, representing the primary indication for surgery. All of the patients were observed for prolonged periods during which optimal nutritional treatment was maintained. Ascites accumulation was prevented by careful salt restriction so that, while considerable amounts of ascites persisted, paracenteses generally were not required. This control of ascitic fluid accumulation does not indicate that the patients selected had a relatively minor tendency to form ascites, since salt restriction can control the formation of ascites in almost every case of cirrhosis.[2,4] In none of the patients was there any decrease in the tendency to accumulate ascites during the prolonged preoperative periods.

Clinical emphasis in each of these five cases is placed on the localization of the abnormal fluid retention before and after the portacaval shunt. Since edema and ascites are a reflection of the abnormal retention of sodium, studies on sodium balance were carried out on each of these patients prior to and following the shunt. For the present purposes estimation of the sodium balance was limited to the determination by dietary calculations of the daily intake of sodium and the daily analysis of the total amount of urinary sodium over prolonged periods. As shown previously, when the tendency to form ascites is strong the urinary excretion of sodium is minimal and is little affected by wide fluctuations in the amount of sodium ingested daily.[2,4,5]

After a suitable period the patients were transferred to the New York Hospital where the portacaval anastomoses were performed using cyclopropane for anesthesia. A week or so later the patients returned to the Rockefeller Institute Hospital for postoperative studies. Each of the patients withstood the surgical procedure remarkably well. Blood transfusions were used liberally throughout the lengthy procedure in order to avoid the risk of further damage to the liver which can be precipitated so easily in such patients by even short periods of shock.

RESULTS

Following portacaval anastomosis the portal venous pressure was reduced in each of the five cases, and within the next month or so ascites completely disappeared. In several instances considerable amounts of fluid were retained abnormally during the postoperative period but, whereas preoperatively such fluid was entirely or primarily in the form of ascites, in the postoperative period it was only in the form of edema. This change in the localization of retained fluid will be stressed in each of the cases presented. In other patients with cirrhosis who had chronic refractory ascites, other surgical procedures did not produce this effect on ascites formation by some non-specific mechanism. In fact, three of these five patients had undergone surgery in the year or two prior to the portacaval shunt and in each case no apparent effect on ascites formation or sodium balance was obtained.

CASE REPORTS

Case 1. M. L. (Fig. 1), a fifty year old woman, gave a history of prolonged nutritional deficiency associated with excessive intake of alcohol, approximating one quart of whiskey daily. When first seen (October 1951) she already had had forty-five paracenteses in the previous year and a half, and some ascites was present for at least six months before the first paracentesis. A large firm nodular liver was easily palpable. She was hospitalized for prolonged periods during the next eighteen months before the portacaval shunt was done. At first, when given a

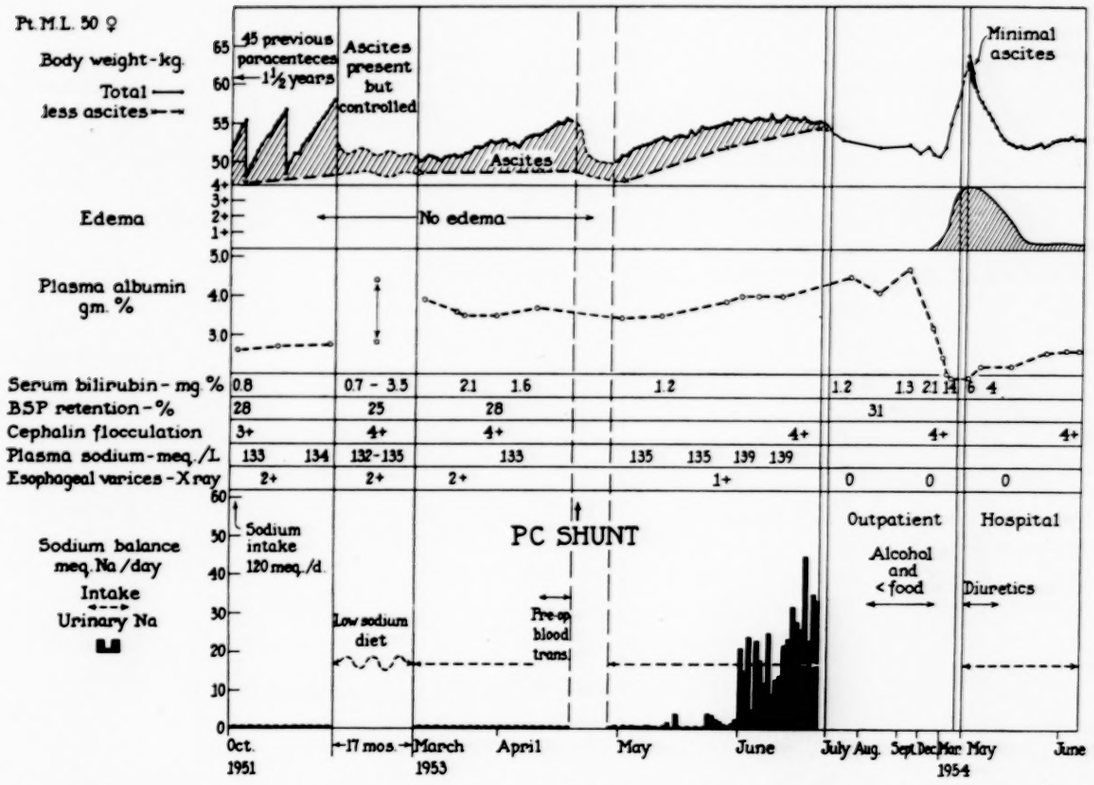


FIG. 1. Maximal ascites before portacaval (PC) shunt, manifested by constant ascites without peripheral edema, and minimal urinary excretion of sodium. Following shunt, the urinary excretion of sodium increased and ascites disappeared. Subsequent hepatic damage resulted in edema without significant ascites.

liberal salt diet, the daily urinary excretion of sodium was invariably less than 1 mEq. despite an intake of 120 mEq. of sodium daily. The retained sodium correlated closely with the average daily accumulation of ascites. Ascites accumulation ceased following a reduction in sodium intake to 17 mEq. daily, but a certain amount of ascites remained. Never was there any indication that the tendency to form ascites had decreased, such as might be reflected in a rise in the daily urinary output of sodium like that usually seen for short periods when a spontaneous diuresis is about to occur. The serum concentration of sodium remained reduced to about the same extent throughout the entire period.

The patient showed virtually no response to mercurial diuretics. Generally, however, she showed some improvement. Serum albumin levels soon rose and averaged 3.8 gm. per cent. After several months' time the patient reached a steady state. She looked fairly well and maintained a good food intake consisting of a low salt diet with a supplement of 70 gm. of powdered protein daily (120 gm. protinal). Two episodes of hematemeses occurred during the following eighteen months because of portal hypertension and ruptured esophageal varices, and on both occasions she responded well to conservative management. Finally in April 1953, after forming ascites maximally for over three years, the patient underwent portacaval anastomosis. The hematemeses justified the procedure despite the presence of refractory ascites. The patient tolerated the procedure well and the portal pressure, measured at the time of the operation, fell from 400 to 280 mm. of saline solution. She returned to the Rockefeller Institute Hospital one week later. During the following three weeks several small fluctuations were seen for the first time in the daily urinary excretion of sodium suggesting that spontaneous diuresis was imminent and finally that urinary sodium exceeded intake. Ascites disappeared completely. A rise in serum sodium concentration also reflected a decreased tendency to form ascites. All these changes occurred while the patient was maintained on the same intake of sodium on which she had been for eighteen months preoperatively. Incidentally, esophageal varices as visualized by x-ray decreased and soon disappeared.

Following disappearance of the ascites the patient returned to a normal salt intake without development of either ascites or edema. The patient felt remarkably well but after several months began to drink considerable amounts of whiskey once again. Her dietary intake rapidly became minimal again and remained so for five months (September 1953 to January 1954), by which time it was apparent that the liver had suf-

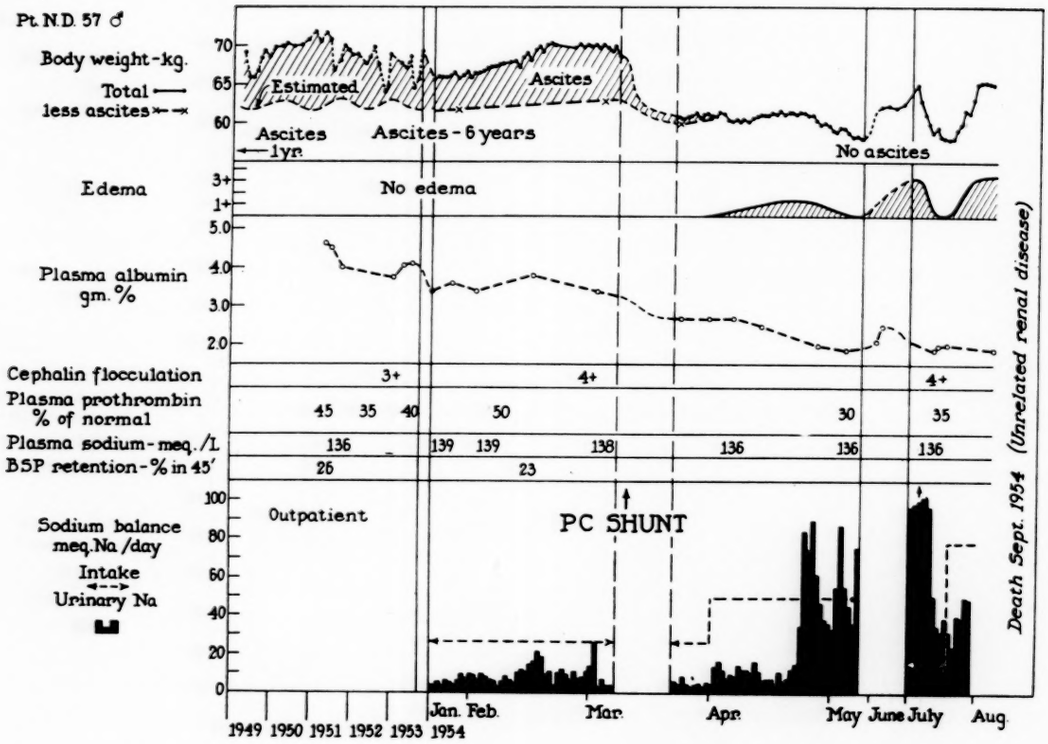


FIG. 2. Persistent ascites for six years disappeared following portacaval (PC) shunt and remained absent despite hypoalbuminemia and peripheral edema formation.

fered further damage. Serum levels of albumin, which had been maintained close to 4 gm. per cent, fell to 1.8 gm. per cent and serum bilirubin rose to 14 mg. per cent. Jaundice had never been prominent before. She finally stopped drinking and returned to a good diet but irreparable damage had apparently been done. Jaundice decreased but, due to persistently low levels of serum albumin, massive edema developed. The legs were so distended that there was some weeping of edema fluid from the skin. In her preoperative years of water and sodium retention no detectable edema had been present. She finally accepted readmission at which time a trace of ascites was detectable for a day or two. Edema was most marked in the legs but some was also present in the upper part of the body. She responded rapidly to salt restriction and mercurial diuretics. The low level of serum albumin persists to the present time. No ascites is present. Because of the hypoalbuminemia the patient now requires a moderately low salt diet. She continues to consume alcohol in variable amounts.

Comments. A patient with advanced Laennec's cirrhosis, demonstrated a maximal tendency to form ascites for three years prior to portacaval anastomosis. Ascites disappeared completely within two months of the shunt. Subsequently, further injury to the liver was suffered and abnormal retention of fluid recurred but as edema fluid instead of ascites.

CASE II. N. D. (Fig. 2), a fifty-seven year old man, gave a history of prolonged dietary insufficiency and consumption of at least a quart of whiskey daily for many years. Finally a typical clinical and laboratory picture of Laennec's cirrhosis developed. A firm irregular liver was palpable. Ascites developed and was constantly present for six years prior to portacaval anastomosis. Accumulation of ascites was controlled by restriction of sodium; in addition the patient maintained a diet made high in protein by supplements of powdered protein of low sodium content (lanolac and protinal). In the fall of 1953 the patient had massive hematemesis, and remained in a comatose state for over one week. He finally responded to intensive treatment which included esophageal tamponade, many blood transfusions, infusions of amino acids and glucose and antibiotics given as a prophylactic measure. Several months later the patient was readmitted in preparation for portacaval anastomosis; esophageal hemorrhage represented the primary indication for surgery since it appeared unlikely that he could survive another such episode. In addition to advanced disease of the liver the patient had arteriosclerotic heart disease which caused episodes of auricular fibrillation. He also had some reduction in function of the kidney with a urea clearance of 50 per cent of normal, but none of the many tests performed revealed abnormalities of the

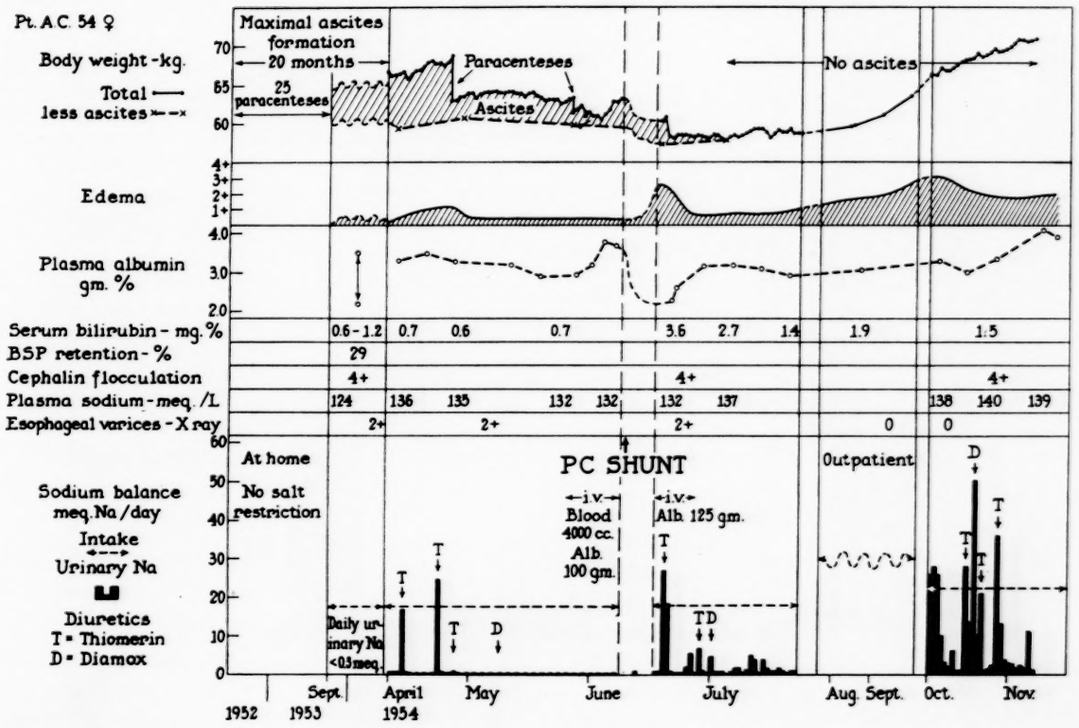


FIG. 3. Maximal ascites for two years disappeared following portacaval (PC) shunt. Peripheral edema, constantly present, became more pronounced after the shunt was established.

urine. Plasma albumin averaged 3.5 gm. per cent which was a little lower than that prior to massive hematemesis.

In March 1954, portacaval anastomosis was performed at the New York Hospital. This resulted in a reduction of portal pressure at the time of surgery from 450 mm. to 260 mm. of saline solution. On his return to the Rockefeller Institute Hospital a small amount of ascites remained but within one week no more ascites was detectable either clinically or by aspiration with a needle. In addition, after doubling the daily intake of sodium no ascites formed. The increased salt intake, however, resulted in the formation of edema which presumably reflected the falling serum level of albumin. Finally, however, by May 1954, the patient lost the edema spontaneously as he maintained a normal sodium balance. At this time he began to have hematuria with some proteinuria but without formed elements other than the erythrocytes in the urine. These renal changes were associated with a rising blood urea nitrogen and a falling urea clearance. Blood pressure remained unchanged. While at home he had a liberal intake of salt, with which about five liters of fluid were retained, but this was entirely edema fluid, and there was no trace of ascites. On moderate salt restriction the edema was rapidly lost but on increasing the intake of salt once again it rapidly reappeared. Gradually the urea nitrogen reached high levels (180 mg. per cent) and finally the patient died of uremia six months after the operation. No apparent relationship between the disease of the kidney and the cirrhosis could be found. Until the time of death no apparent changes in hepatic function occurred.

Comments. This patient with advanced Laennec's cirrhosis had had chronic ascites constantly for six years prior to the shunt operation without peripheral edema. Following the shunt, ascites promptly disappeared and did not recur despite hypoalbuminemia. Peripheral edema developed postoperatively. He died of apparently unrelated disease of the kidney.

CASE III. A. C. (Fig. 3), a fifty-four year old woman, had a history of dietary insufficiency associated with steady consumption of excessive amounts of whiskey for many years. When first seen in September 1953, she already had had twenty-five paracenteses and showed all of the usual clinical and laboratory manifestations of Laennec's cirrhosis. The urinary excretion of sodium was minimal, amounting to less than 1 mEq. of sodium daily irrespective of the amount of sodium ingested. The accumulation of ascites was controlled by restriction of sodium intake to 17 mEq. daily, but a considerable amount of ascites was consistently present. Some edema of the legs appeared preoperatively and was considered to be due to high venous pressure in the legs caused by the constant presence of ascites, although in view of the subsequent course this explanation may not be satisfactory. The patient had two episodes of melena

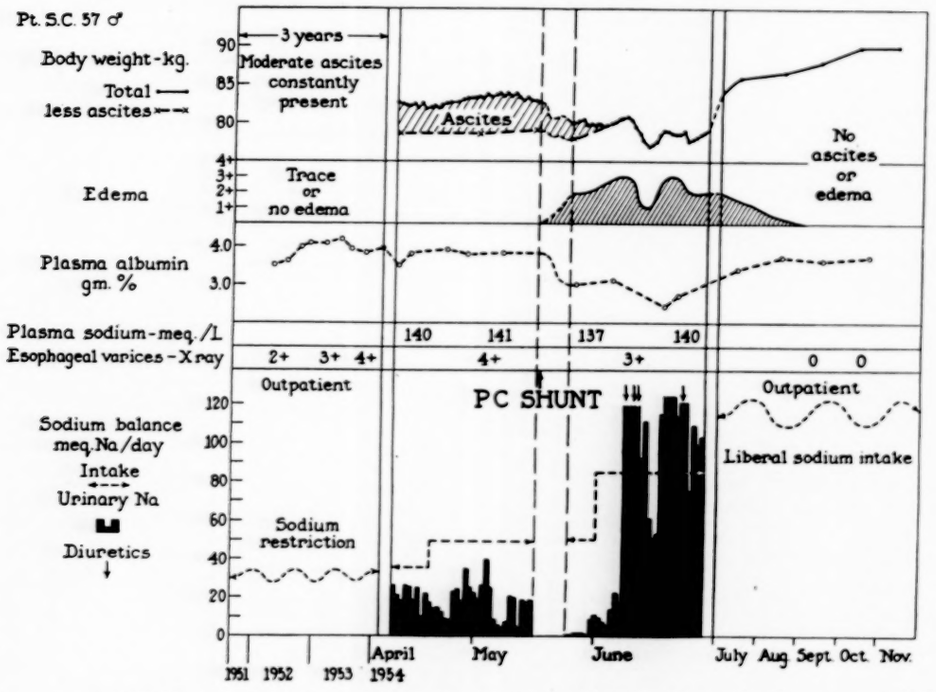


FIG. 4. Prior to portacaval (PC) shunt ascites was present, without peripheral edema, for three years. Following shunt peripheral edema was present without ascites until the serum albumin rose; edema then disappeared despite increase to normal salt intake.

resulting in marked anemia but she had no frank hematemesis.

Esophagrams showed esophageal varices and the gastrointestinal bleeding was considered to be from the esophageal varices. Serum albumin averaged 3.0 gm. per cent. Preoperatively the patient was given large amounts of blood and concentrated human serum albumin, which had no effect on the ascites or on the urinary excretion of sodium. Portacaval anastomosis was performed at the New York Hospital, and the portal pressure measured at the time of the operation fell from 460 mm. to 340 mm. of saline. A slight elevation in serum bilirubin was noted but otherwise there were no ill effects from the operation. Within two weeks after her return to the Rockefeller Institute Hospital the ascites had completely disappeared, although the peripheral edema increased. Urinary excretion of sodium, which preoperatively was constantly less than 1 mEq. a day, showed some increase but no pronounced diuresis of sodium occurred. Thus the major change which followed surgery was the disappearance of ascites after having been present maximally for almost two years.

While in a convalescent home the patient was doing well but she began to drink whiskey again intermittently, although only for several weeks. Edema became a major problem and it occurred despite levels of serum albumin which averaged 3.3 gm. per cent. The remainder of the tests of hepatic function remained steady. Since edema was confined to the legs some change was suspected in the hemodynamics of the lower extremities, possibly secondary to the shunt. Venous pressures in both femoral veins were within normal limits however. Since the patient had advanced osteoporosis, she was receiving various hormones but edema persisted when all medications were discontinued. Even when edema became extreme, no ascites was detectable.

In December 1954, the patient developed an intestinal obstruction with minimal symptoms. Surgical correction was contemplated but she went into hepatic coma and surgery at that time could not be considered. By means of a Miller-Abbott tube, antibiotics and the constant infusion of amino acids and glucose the patient survived for two weeks. By then the obstruction had partially cleared and consciousness barely returned. However, hepatic damage had been increased by this episode and staphylococcus septicemia resulted in death. Autopsy showed a tight adhesion about a loop of small intestine with a lumen that was about 2 mm. patent. The area was surrounded by local tissue hemorrhage. No ascites was present except for several hundred cubic centimeters of bloody fluid.

Comments. This patient had had advanced Laennec's cirrhosis and maximal ascites for almost two years prior to portacaval anastomosis. Ascites disappeared after the shunt. Peripheral edema, the cause of which was not completely understood, was present throughout.

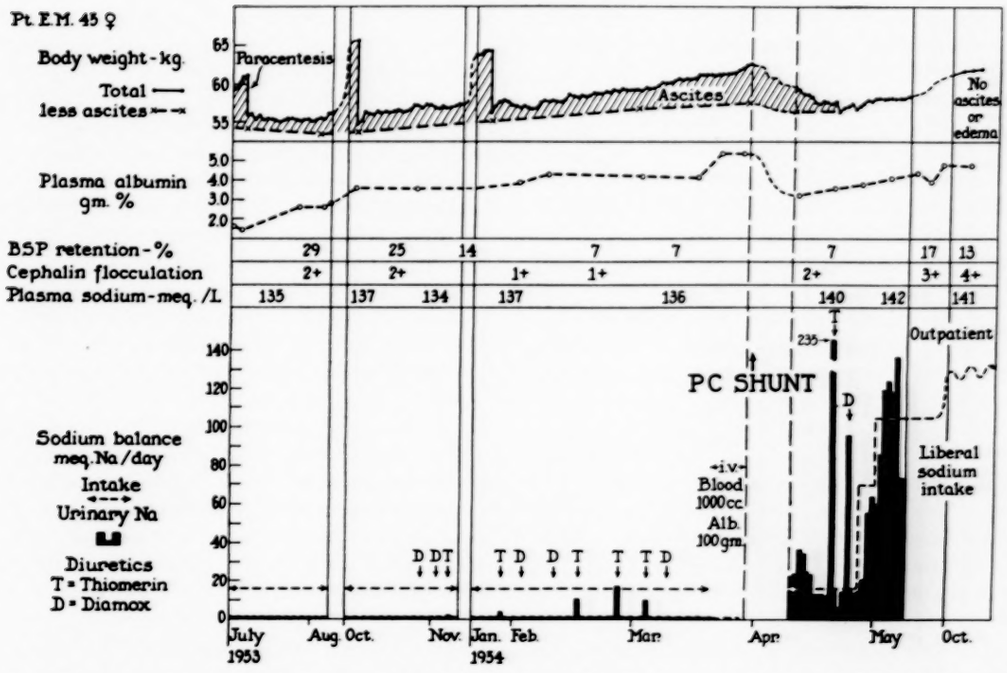


FIG. 5. Ascites disappeared promptly after portacaval (PC) shunt despite increase to normal intake of salt. Response to diuretics, which was insignificant before shunt, became normal thereafter.

CASE IV. S. C. (Fig. 4), a fifty-seven year old man, was found to have all the clinical and laboratory manifestations of Laennec's cirrhosis following the appearance of ascites in 1951. The cause, however, remains obscure. He had not had a heavy alcoholic intake but he drank wine in moderation. No history of hepatitis was noted. Dietary intake, while low in protein, could not be considered deficient by ordinary standards. Accumulation of ascites was controlled by salt restriction so that paracentesis were not required. However, the abdomen was constantly distended with at least several liters of ascitic fluid. Concentration of serum albumin remained fairly satisfactory, averaging 4.0 gm. per cent. Esophageal varices became extremely large and extended to the upper esophagus. Otherwise the patient remained in good condition.

In May 1954, portacaval anastomosis was performed and the portal pressure fell from 450 mm. to 260 mm. of saline solution, measured at the time of the operation. Within one week after his return to the Rockefeller Hospital no ascitic fluid was detectable either clinically or by aspiration with a needle. Even after being given a liberal intake of sodium no ascites was noted, although marked peripheral edema and hypoalbuminemia developed. Edema persisted for a short period until the patient's postoperative hypoalbuminemia improved. Since then he has had neither edema nor ascites and has gained considerable weight.

Comments. This patient with Laennec's cirrhosis had chronic ascites which was constantly present for 3 years. Ascites promptly disappeared following the portacaval shunt. During the immediate postoperative period the patient retained water abnormally but it was entirely in the form of peripheral edema.

CASE V. E. M. (Fig. 5), a forty-five year old woman, developed ascites in the spring of 1953. She had a history of recurrent diverticulitis, with abscess formation, and resection of the involved area. In addition, there was a history of moderate alcoholic intake. At the onset of ascites the liver was palpable and firm, and laboratory tests and liver biopsy specimen taken later confirmed the diagnosis of Laennec's cirrhosis. Spider telangiectases were present.

Following hospitalization in July 1953, the patient showed considerable improvement. The plasma albumin reached concentrations averaging 3.6 gm. per cent. It was considered likely that a spontaneous diuresis would eventually occur. However, she constantly required careful restriction of sodium to prevent an increase in ascites. On each occasion, when she was at home, a slightly increased salt intake resulted in an increase in ascites so that occasional paracenteses were necessary. She showed virtually no response to diuretics, including thiomerin and diamox.® Serum sodium was always slightly depressed or at least on the low side of normal, suggesting a strong tendency to form ascites. Esophageal varices were visualized on x-ray examination. The patient was becoming depressed at the lack of apparent improvement; her general spirits became poor and her food intake began to wane. Thus after having had

ascites of a maximal type for one year the patient underwent portacaval anastomosis. The portal pressure fell from 280 mm. to 170 mm. of saline solution. One week after return to the Rockefeller Institute Hospital no ascites was detectable either clinically or by needle aspiration, nor has any been present subsequently despite return to a diet high in salt (estimated at 10 to 15 gm. per day). This change in the tendency to retain salt and water is reflected in the sodium balance. Whereas previously there had been practically no response to diuretics, following the shunt she showed a normal sodium diuresis to both thiomerin and diamox. The daily urinary excretion of sodium, which in the preshunt period averaged less than one mEq., spontaneously rose to levels which exceeded the intake of sodium. No edema was present at any time in this patient. Following the shunt she showed a gain in weight.

Comments. Immediately following a portacaval shunt ascites disappeared after having been present maximally for one year. One cannot say that this diuresis would not have occurred spontaneously, but the time relationships and the immediate completeness of the diuresis suggest that it resulted from the portacaval shunt.

In contrast to the five cases cited, in which chronic ascites disappeared following the portacaval shunt, the following two cases present patients who developed ascites for the first time immediately after portacaval anastomoses. These cases are presented because they contribute to the discussion of the problem.

CASE VI. E. M., an eighteen year old girl, three years prior to the portacaval anastomosis developed what was considered to be a fairly mild episode of infectious hepatitis. However, it soon became evident that cirrhosis was present. The cirrhosis resembled that observed in a group of adolescent girls, namely a coarsely nodular cirrhosis with greatly altered hepatic architecture, large nodules of liver cells and broad bands of scar tissue. Patients with this disease look remarkably well. For considerable periods they remain well nourished and relatively asymptomatic. They have many telangiectases, hepatic fetor and minimal jaundice. One unusual feature in this group is the markedly elevated level of serum γ-globulin which is found. This patient had a total protein of 11 gm. per cent including 8 gm. per cent globulin of which 7.2 gm. per cent was γ-globulin. Finally, after remaining in a steady state for some time, she sustained a massive esophageal hemorrhage which recurred three weeks later. On the second occasion bleeding was difficult to control so that esophageal tamponade had to be continued until a portacaval anastomosis was performed (New York Hospital).

The portal pressure at the time of operation fell from 380 mm. to 140 mm. of saline solution; at this time an unusual amount of lymphatic drainage from the porta hepatis was noted. Several days later it became apparent that ascites was forming rapidly and, until her death several weeks later, ascites formation and the associated dehydration elsewhere in the body were the major problems. It was obvious that the tendency to form ascites was more extreme than that encountered in the presence of the usual type of advanced Laennec's cirrhosis. The relentlessness of ascites formation was reflected in peripheral dehydration and in steadily falling levels of serum sodium, which leveled off at approximately 110 mEq. per liter. For several days while in the surgical ward the patient was given large doses of sodium (300 to 500 mEq. per day) and nothing but transitory effects occurred on the level of serum sodium. These large doses of salt resulted in a proportionate increase in the ascites formation, and consequent depletion of plasma proteins. The latter, however, was checked by daily administration of 25 to 50 gm. of human albumin. Each time a paracentesis was performed the peripheral state of dehydration increased and shock developed. This was largely avoided by increasing the amount of albumin or blood administered prior to, during and after each paracentesis. Finally, however, such control became impossible when a spontaneous leak of ascitic fluid occurred so that continuous paracentesis resulted. Shock, which soon followed, could not be controlled even with large amounts of serum albumin and blood. Death soon occurred.

This extreme degree of ascites formation hitherto had been seen by us only in patients with Chiari's syndrome. Here, however, another possibility was that it was due to thrombosis of the recent portacaval shunt. However, at autopsy the shunt was found to be widely patent so that portal pressure throughout the mesentery was probably within normal limits. While there was no hepatic vein obstruction (Chiari's syndrome), there was diffuse and marked endophlebitis of the hepatic venules. Thus, in retrospect, it appears likely that a situation equivalent to the classic Chiari syndrome was present in that venous drainage from the liver was partially obstructed and the increased intrahepatic venous pressure caused extravasation of excessive fluid into the lymphatic system and into the peritoneal space.

CASE VII. A. C., a fifty-six year old man with typical Laennec's cirrhosis underwent a portacaval anastomosis for esophageal hemorrhages. Prior to establishment of the shunt ascites was never detected. At operation minimal ascites was found and, again, an unusually large amount of fluid oozed from the porta hepatis, possibly representing leakage of hepatic lymph from surgically injured lymphatics. On the basis of this observation the formation of ascites was anticipated. Several days postoperatively ascites formed rapidly (1 L. per day). Replacement of salt and albumin in amounts approximating that lost into the ascitic fluid prevented too great a depletion of serum sodium and albumin. After about four days the forma-

tion of ascites ceased and the remaining ascites was promptly reabsorbed, and none reformed later. Although one can only speculate, it appears reasonable to suggest that this ascitic fluid represented leakage from hepatic lymphatics severed in the portal hepatic area, and termination of ascites occurred when the lymphatics became reestablished. Possibly this is a frequent occurrence but is only manifested in cases in which, for various reasons, hepatic lymph flow is exceptionally profuse.

Comments. These two patients have in common formation of significant ascites for the first time following portacaval anastomosis despite a lowering of the portal blood pressure. In both instances at surgery an increased flow of fluid, presumably hepatic lymph, was noted in the porta hepatis.

In Case VI, exhibiting endophlebitis of the hepatic veins and presumably normal portal blood pressure, the mechanism of ascites formation was approximately that in dogs in which supradiaphragmatic obstruction of the vena cava is produced and this causes increased hepatic venous pressure and ascites without necessarily being accompanied by portal hypertension.

The temporary formation of ascites in Case VII suggests the possibility that surgical trauma, such as the severance of lymphatics draining the hepatic lymph, may account for the appearance of ascites which persists only for a week or so. Some such mechanism may also account for the variation in the time required for reabsorption of ascites following shunt operations in patients with chronic ascites, as exemplified in Cases I to V.

OBSERVATIONS

Reduction in portal hypertension by means of portacaval anastomosis resulted in the disappearance of ascites in five patients with Laennec's cirrhosis in whom ascitic fluid had been constantly present for from one to six years. Such a response has not been noted in similar patients with refractory ascites following other surgical procedures. Of even more significance than the disappearance of the ascites was the continued absence of ascites despite the development of marked peripheral edema in several patients at some time following the shunt. The edema was usually associated with hypoalbuminemia. Thus in these patients in whom portal hypertension was no longer extreme abnormal retention of salt and water resulted in the formation of peripheral edema, occasionally massive, but without ascites. Thus the intra-abdominal localization of retained fluid was no longer present. As a result of these observations it was apparent that a basic change in the mechanism of ascites formation had been effected by means of portacaval anastomosis. These observations give further support to the concept previously discussed, that in patients with chronic ascites due to Laennec's cirrhosis the various mechanisms which account for abnormal retention of sodium and water by the kidney are secondary to, rather than the cause of, ascites.[2]

The series of events which followed portacaval anastomosis form rational sequence only if portal hypertension plays an important role in the development of ascites in patients with Laennec's cirrhosis. It is important to realize that portacaval anastomosis causes a reduction in portal venous pressure not only in the extrahepatic portal system but throughout the extensive intrahepatic portal system as well. This point is often overlooked when the portal hypertension of Laennec's cirrhosis is considered in the same terms as portal hypertension due to an extrahepatic block in the portal vein. In patients with Laennec's cirrhosis the portal pressure prior to the shunt is elevated in both the intrahepatic and the extrahepatic segments of the portal venous system, the latter often above 400 mm. of saline solution. Such pressures applied to veins elsewhere in the body cause the development of edema. There is no apparent reason to consider that the capillaries throughout the portal system handle fluid differently from those elsewhere. Thus one may expect that with increasing portal pressure more and more fluid would transfer from the vascular compartment into the extravascular space of the mesentery and thence into the lymphatic draining the area. With high pressures a point is reached at which, due to the increased transfer of fluid, lymphatic drainage becomes inadequate and ascites forms as edema forms in the periphery. With extreme elevation in pressure in the extrahepatic portal system, edema in the wall of the intestine is occasionally observed directly at postmortem examination and even on x-ray examination of the abdomen.

A similar situation probably applies throughout the extensive segment of the portal system which is intrahepatic. Increased pressure in this latter section of the portal systems presumably leads to increased formation of hepatic lymph, resulting in increased pressure within the lymphatics. Some evidence exists to suggest that at least in certain patients with Laennec's cirrhosis there is some transfer of lymph from the liver directly into the ascitic fluid, thus increasing the accumulation of ascites.[6] Also, as a result of increased flow of hepatic lymph into the

thoracic duct, the capacity for reabsorption of ascitic fluid by the lymphatic system may be proportionately reduced.

No evidence exists that venous hypertension in Laennec's cirrhosis extends beyond the portal system into the hepatic venous system. In Laennec's cirrhosis there are no distended hepatic veins or central veins or sinusoids such as one expects to see if hepatic venous pressure is significantly increased. On the other hand, in cases in which there is markedly elevated pressure in the hepatic veins and hepatic sinusoids extravasation of fluid from the vascular compartment into the hepatic lymphatic system increases greatly.[7] With obstruction in the hepatic veins large amounts of ascites presumably form directly from the fluid exuding from the surface of the liver which is derived from the hepatic lymphatics. This situation is analogous to that which is produced experimentally in dogs by supradiaphragmatic ligation of the inferior vena cava, whereupon fluid may actually be seen forming on the surface of the liver.[1] Clinically this picture of ascites formation due to hepatic vein hypertension is produced by congestive heart failure, constructive pericarditis, tricuspid insufficiency, obstruction in the inferior vena cava and hepatic vein thrombosis (Chiari's syndrome). In this group ascites may form, even to an extreme degree, while the portal pressure may be within normal limits. Similarly, in a case herein presented (Case VI), ascites formed extremely rapidly despite the almost certain absence of marked portal hypertension (large patent shunt at autopsy) but a diffuse endophlebitis of the hepatic veins was found at autopsy, so that the hemodynamics of Chiari's syndrome were at least approximated. It would seem that the experiments on dogs, in which ascites is produced secondary to obstruction in the hepatic vein, so highly regarded in current discussions on the pathogenesis of ascites, really have a limited application. These experiments on dogs bear only remotely on the problem of the formation of ascites in Laennec's cirrhosis in which there is no satisfactory evidence of hypertension in the hepatic veins, central veins or sinusoids.

A final comment may be made regarding the temporary development of ascites which occasionally occurs following portacaval anastomosis. The patient who illustrates this point (Case VII) never had detectable ascites previously. More frequently, however, postoperative ascites occurs in patients who have previously had ascites that has disappeared only to recur immediately after portacaval shunt and other surgical procedures. The fact that in some cases, fortunately few, ascites may appear temporarily despite the lowering of portal pressure by the shunt might be considered an argument against the importance of portal hypertension in the development of ascites. Here again, however, as is suggested by the relatively rapid sequence of development and disappearance of ascites, one is probably dealing with a mechanism of ascites production which differs from that accounting for the chronic formation of ascites in Laennec's cirrhosis. One can only speculate regarding the pathogenesis of this acute form of ascites. In the course of the procedure numerous lymphatics which drain hepatic lymph are cut or blocked in the dissection in the area of the porta hepatis, so that large amounts of clear hepatic lymph may flow directly into the peritoneal cavity or from the hepatic surface if the lymphatics are blocked. Shortly after surgery these lymphatics are reestablished, ascites no longer forms, and that which is present rapidly disappears. Why this occurs only in certain patients may depend on the quantity of hepatic lymph which is formed. Thus in one case cited (Case VII) during the dissection in the porta hepatis much more lymphatic oozing was noted than is usually encountered. Such a mechanism incidentally might explain the variable time which elapsed following the shunts before ascites disappeared in the five patients with chronic ascites.

In summary, then, it is suggested that these clinical results re-emphasize the importance of the role of portal hypertension in the pathogenesis of ascites in chronic Laennec's cirrhosis. It is felt that the data presented here supporting this position are more direct and presumably more applicable to the problem than many of the observations made in animal experiments cited in support of the opposing view.

A more direct method of studying the relationship of portal hypertension and ascites formation, so long sought, may now be available by employing percutaneous splenic puncture and measuring intrasplenic venous pressure.[8] On the basis of preliminary observations this pressure corresponds closely to portal pressure. If the identity of these pressures is confirmed and if the procedure is as innocuous as it appears to be at present, one may follow patients serially and relate the portal pressure to the tendency to

accumulate ascites. Until results from such a study become available the precise relationship of portal pressure and ascites formation must remain in the present state of speculation.

SUMMARY

The effect of portacaval anastomosis on the fluid and electrolyte balance of five selected patients with Laennec's cirrhosis and chronic ascites was studied. In these persons ascites disappeared following the shunt operation, although marked peripheral edema developed in several cases. These observations are presented in support of the importance of the role of portal hypertension in the formation of ascites in Laennec's cirrhosis.

Portacaval anastomosis is not advocated as a general method of treating chronic ascites, although it may be beneficial in some patients.

In two additional patients cited ascites made its first appearance shortly after portacaval anastomosis was established. A possible mechanism is postulated.

The formation of ascitic fluid in experimental animals in whom hepatic venous pressure is elevated is also discussed. It is considered that these results apply to the formation of ascites in certain clinical conditions but do not necessarily apply in the case of Laennec's cirrhosis.

REFERENCES

1. Hyatt, R. E. and Smith, J. R. The mechanism of ascites. *Am. J. Med.*, 16: 434–448, 1954.
2. Eisenmenger, W. J. Role of sodium in the formation and control of ascites in patients with cirrhosis. *Ann. Int. Med.*, 37: 261–272, 1952.
3. Volwiler, W., Grindlay, J. H. and Bollman, J. L. The relation of portal vein pressure to the formation of ascites—an experimental study. *Gastroenterology*, 14: 40–55, 1950.
4. Eisenmenger, W. J., Blondheim, S. H., Bongiovanni, A. M, and Kunkel, H. G. Electrolyte studies on patients with cirrhosis of the liver. *J. Clin. Investigation*, 29: 1491–1499, 1950.
5. Farnsworth, E. B. and Krakusin, M. S. Electrolyte partition in patients with edema of various origins. *J. Lab. & Clin. Med.*, 33: 1534–1544, 1948.
6. Eisenmenger, W. J. and Slater, R. J. Metabolism of albumin in patients with hepatic cirrhosis. Transfer of albumin-I^{131} and albumin-T 1824 across vascular and peritoneal membranes. In preparation.
7. Nix, J. T., Mann, F. C., Bollman, J. L., Grindlay, J. H. and Flock, E. V. Alterations of protein constituents of lymph by specific injury to the liver. *Am. J. Physiol.*, 164: 119–122, 1951.
8. Atkinson, M. and Sherlock, S. Intrasplenic pressure as index of portal venous pressure. *Lancet*, 266: 1325–1327, 1954.

Studies in Ammonia Metabolism*

I. Ammonia Metabolism and Glutamate Therapy in Hepatic Coma

B. Eiseman, M.D., W. Bakewell, M.D. *and* G. Clark, M.D.
Denver, Colorado

An elevated blood ammonia concentration is one of the many abnormalities noted in hepatic failure and has been considered the factor producing neurologic symptoms typical of hepatic coma.[1–3,6,18,27,28] Recently it has been shown that blood ammonia levels raised by feeding ammonium salts to patients[4,5,10,11,15,18,31] or animals[14–16] with liver disease, or to men with portacaval anastomoses,[14,22] will precipitate episodes of unconsciousness similar to those seen in hepatic coma.

In an effort to diminish blood ammonia concentrations in hepatic coma, sodium glutamate has been given clinical trial and reported to be of therapeutic value.[21,25,26,28,32]

The purpose of this study is to report our experience in the measurement of blood ammonia concentrations in animals and man in hepatic coma, to evaluate the therapeutic effect of glutamate and, on the basis of these studies, to differentiate those cases of hepatic coma precipitated by ammonium salt ingestion from those in which coma develops spontaneously in the course of progressive hepatic failure.

Table I
Summary of Patients Included in Study

Normal without liver disease	25
Cirrhosis without coma	15
Alcoholic cirrhosis (11)	
Infectious hepatitis (4)	
Cirrhosis in coma	31
Alcoholic cirrhosis (27)	
Infectious hepatitis (4)	

MATERIALS AND METHODS

Blood ammonia concentrations have been determined in twenty-five normal patients, fifteen patients with advanced cirrhosis not in coma and in thirty-one patients in forty-four episodes of hepatic coma. (Table I.) These patients (fifty-two men and nineteen women) were from the wards of the three University of Colorado Hospitals in Denver and ranged in age from twenty-three to seventy-one. Ammonia concentrations were measured by the Conway micro-diffusion method[7] or according to the technic of Seligson and Hirahara.[24] The Conway method has proven to be more accurate and is now used exclusively. The etiology of cirrhosis in the comatose group was chronic alcoholism in twenty-seven patients and acute infectious hepatitis in four persons. The acute factors precipitating coma are summarized in Table II. Essentially all stages of hepatic coma were observed in this series but only those patients with cirrhosis who demonstrated a depressed level of consciousness, abnormal neurologic motor signs (usually flapping tremor) or convulsions were included. Other signs and symptoms of cirrhosis, such as jaundice, ascites, portal hypertension, fetor hepaticus and derangement of liver function tests, were present in variable degrees. Three patients in a comatose state who had cirrhosis with marked hyponatremia were excluded from this study; in each case the coma disappeared rapidly after sodium administration.

Table II
Factors Precipitating Coma*

Ammonium salt ingestion	7
Gastrointestinal bleeding	6
"Spontaneous" progressive liver failure	18

* Coma precipitated by paracentesis and characterized by hyponatremia not included.

Experimental hepatic coma was produced in four dogs by ligating the hepatic artery thirty-six hours after the creation of an end-to-side portacaval shunt according to the method of Rappaport.[12,20] Blood ammonia determinations were made at six- to twelve-hour intervals until the dog died between the first and third day.

Ammonium citrate, 15 gm., was given by mouth to six patients who had had portacaval vascular shunts and whom blood ammonium concentrations had

* From the Departments of Surgery and Medicine, University of Colorado Medical School and the Veterans Administration Hospital, Denver, Colorado. Supported in part by a United States Public Health Grant.

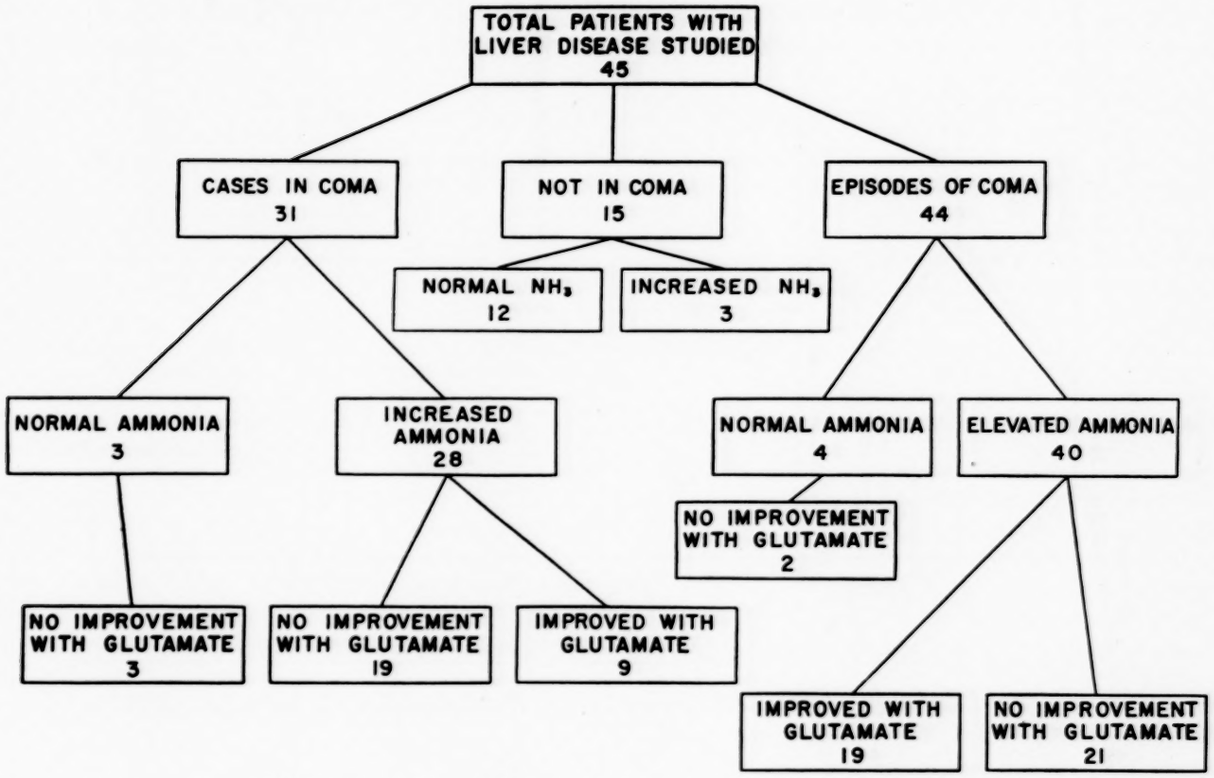

TOTAL PATIENTS WITH LIVER DISEASE STUDIED 45
CASES IN COMA 31
NOT IN COMA 15
EPISODES OF COMA 44
NORMAL NH_3 12
INCREASED NH_3 3
NORMAL AMMONIA 3
INCREASED AMMONIA 28
NORMAL AMMONIA 4
ELEVATED AMMONIA 40
NO IMPROVEMENT WITH GLUTAMATE 2
NO IMPROVEMENT WITH GLUTAMATE 3
NO IMPROVEMENT WITH GLUTAMATE 19
IMPROVED WITH GLUTAMATE 9
IMPROVED WITH GLUTAMATE 19
NO IMPROVEMENT WITH GLUTAMATE 21

FIG. 1. Ammonia metabolism and glutamate therapy in liver disease.

been determined at thirty-minute intervals for three hours thereafter. Similar tests were done on six dogs under similar conditions after the administration by stomach tube of 7 gm. of ammonium citrate.

L-Monosodium glutamate* was administered intravenously to patients in coma in daily doses of 23 gm., dissolved in 1 L. of 5 per cent glucose in water. In order to minimize loss in the urine five hours or more were taken for each infusion.

RESULTS

Blood Ammonia Levels. Control blood ammonia levels in our hands varied between 0.9 to 2.0 μg. per ml. Duplicate determinations simultaneously performed on each freshly drawn (within ten minutes) blood sample gave a reproducible maximum variation of less than 5 per cent. Agreement occurred between the ammonia concentrations as determined by the Conway[7] and Seligson[24] technic.

The blood ammonia concentrations in patients with marked cirrhosis who were not in coma were within normal limits in twelve of fifteen patients so studied. (Fig. 1.) In three patients ammonia levels were elevated without accompanying abnormal neurologic signs or depression of the sensorium. One fifty-four-year old patient who had typical alcoholic cirrhosis, jaundice and ascites and who on laboratory examination showed evidence of severe liver damage had a blood ammonia level of 3.3 μg per ml. and 3.4 μg per ml. on two successive days, yet was completely responsive and alert and showed no abnormal neurologic signs. Thereafter the ammonia levels fluctuated from this maximum to within normal limits, yet the cirrhosis was not complicated by unconsciousness, convulsions or tremor.

Of the thirty-one patients in hepatic coma, twenty-eight (87 per cent) had blood ammonia concentrations greater than our maximum normal of 2.0 μg. per ml. The mean ammonia concentration in the group of patients in a comatose state was 3.1 μg./ml. Four patients had more than one episode of coma, and one person lapsed into coma on seven separate occasions. Blood ammonia levels were elevated above the maximum normal in forty of the forty-four observed episodes of coma. Three patients in typical hepatic coma had consistently

* Supplied by Mr. B. F. Buchanan, Pharmaceutical Department, Amino Products Division, International Minerals and Chemicals Corporation.

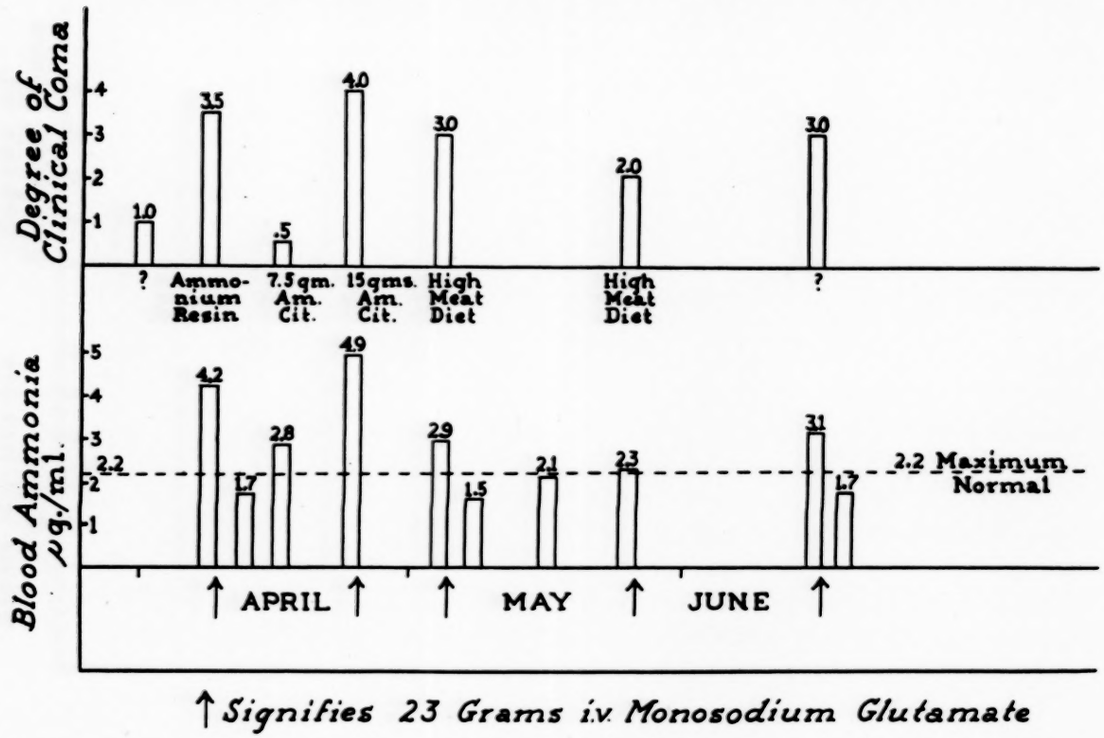


FIG. 2. Patient C. W. (Hospital No. 300431). Relation of episodic hepatic coma to blood ammonia levels and glutamate therapy.

normal blood ammonia levels despite a fatal outcome in two instances.

The clinical course, as well as multiple blood ammonia determinations, has been followed in thirty-one patients in hepatic coma. It is our clinical impression that the course of the coma in most instances is reflected in the fluctuation of the blood ammonia levels. Figure 2 illustrates such a case in which episodic coma was reflected on five occasions by an elevated blood ammonia level.

Each of four dogs in hepatic coma induced by the method of Rappaport[20] showed progressively increasing blood ammonia concentrations as they passed into convulsions and coma and died.

Ammonium Citrate Tolerance Tests. The ingestion of ammonium citrate by normal patients caused no elevation in blood ammonia concentration. In patients with cirrhosis, consistent elevations to a median peak of 3.6 μg. per ml. occurred thirty to sixty minutes following ingestion of ammonium salt, with return to normal levels within two hours. In one patient ingestion of 15 gm. of ammonium citrate resulted in early signs of hepatic coma, that is, twitching, flapping tremors of the hands, drowsiness and a decreased level of consciousness. Spontaneous recovery occurred within six hours.

All the animals and patients with patent portacaval anastomoses demonstrated a marked and prolonged rise in peripheral blood ammonia following oral intake of ammonia citrate. The significance of this fact as a test for patency of a portacaval vascular shunt is discussed elsewhere.[8] In one patient 7 gm. of oral ammonium citrate produced no adverse clinical effects, whereas 15 gm. given three days later was followed by a light-headed sensation, drowsiness and a decreased level of consciousness; an electroencephalographic tracing showed an abnormal slow dysrhythmia interpreted as typical of the electroencephalogram pattern of hepatic coma.[9,21]

Glutamate Therapy. In accordance with previous trials by others,[28] intravenous sodium glutamate was given to thirty-one patients in a total of forty-four episodes of hepatic coma. Such therapy is based on the combination of glutamic acid with ammonia in the formation of glutamine.[30] Beneficial results as judged by disappearance or marked improvement of the coma within twelve hours after drug administra-

tion was noted in nine cases (29 per cent). (Table III.) In all but one of the cases hepatic coma, responding favorably by these criteria to glutamate therapy, had been precipitated either by ingestion of ammonium salts, a high protein diet, or by upper gastrointestinal bleeding. Only

TABLE III

EFFECT OF GLUTAMATE ADMINISTRATION OF HEPATIC COMA

Number of comatose patients receiving glutamate intravenously	31
Number of patients demonstrating benefit following therapy	9 (29%)
Precipitating factor in coma of patients so benefited:	
Ammonium salt or high protein ingestion	6
Upper gastrointestinal bleeding	2
"Spontaneous" progressive hepatic failure	1

one patient so benefited had spontaneously lapsed into unconsciousness during progressive hepatic failure. In all of these patients other non-specific therapeutic measures were being employed, such as high caloric, high vitamin infusions, cortisone and aureomycin therapy, and correction of fluid and electrolyte deficiencies.

In five patients recurring episodic stupor characterized the clinical course of the hepatic disease. One patient in this group (Fig. 2) was observed in six such episodes of stupor. Each episode, induced by ingestion of ammonium salts or excess protein ingestion, was accompanied by an elevation in the blood ammonia concentration and responded well to intravenous glutamate therapy. No reliable distinguishing clinical or chemical factor was noted that differentiated these patients who had intermittent episodes of coma from the larger group of patients in whom coma was a spontaneous complication of hepatic failure and who were resistant to therapy.

Neither depth of coma nor blood ammonia elevation was of absolute prognostic significance in predicting response to glutamate therapy. Of the nine patients in a comatose state who responded to glutamate therapy, all had elevated blood ammonia levels.

Nineteen cirrhotic patients in a comatose state were observed whose blood ammonia levels were markedly elevated but whose fatal course was in no way altered by glutamate administration. During and immediately after glutamate infusions blood ammonia levels were depressed toward normal, but upon termination of the infusion ammonia levels rose to the previous high concentration.

The raised blood ammonia concentrations in the two dogs and three patients with portacaval anastomoses given oral ammonium citrate were in no way changed by sodium glutamate administration.

COMMENTS

Much of our data supports the currently popular thesis that hepatic coma is the result of ammonia intoxication.[5,13,14,16,17,19,23,26,29,32] These facts may be summarized as follows: (1) A majority (twenty-eight of thirty-one, or 90 per cent) of our patients in hepatic coma had elevated blood ammonia concentrations. (2) The blood ammonia concentrations in these patients generally paralleled the clinical course of coma. (3) Elevation in peripheral blood ammonia paralleled the clinical course of hepatic coma in experimentally induced hepatic failure in dogs. (4) Hepatic coma was precipitated in the cirrhotic animal and man by an oral ammonium salt load sufficient to elevate peripheral blood ammonia concentrations. (5) An excessive protein or ammonium salt intake in animals or in man with portacaval anastomoses produced temporary elevations in blood ammonia concentrations accompanied by coma similar to that associated with hepatic failure.

However, a significant number of patients in this study deviate from the close positive correlation between hepatic coma and increased blood ammonia concentration to warrant more critical examination of the attractive theory that hepatic coma is simply a matter of ammonia intoxication. In three patients typical hepatic coma occurred in the presence of normal concentrations of blood ammonia. On the other hand, three patients with persistently elevated blood ammonia levels of a degree usually associated with coma showed no depression of the sensorium or neurologic deficit. Such discrepancies have been explained[27,28] by the fact that blood ammonia concentrations are extracellular measurements, not indications of the more significant intracellular concentrations. Since we have no method for measuring intracellular ammonia concentrations, this hypothesis is unproven.

A more likely explanation is that ammonia intoxication may be only one of several mechanisms capable of producing coma in disease of the liver and that an elevated peripheral blood ammonia concentration may merely reflect a

metabolic dysfunction of more fundamental importance.

It appears that there are at least two types of coma that may be associated with disease of the liver or portal venous diversion around the liver. In one group coma appears spontaneously as a complication of progressive hepatic failure, usually is not affected by glutamate therapy and has an extremely poor prognosis. In the other group coma is precipitated by ingestion of excessive amounts of protein or ammonium salts, is associated with high blood ammonia levels for short periods of time and usually disappears concomitantly with the administration of glutamate. The latter group appears to be pure ammonia intoxication; the former may represent a more complicated metabolic disorder.

Glutamate has been of little therapeutic value in the majority of cases of hepatic coma included in this study. Its value in the management of coma precipitated by exogenous ammonia administration is of questionable significance since such coma is the direct result of an acute chemical insult which subsequently is withdrawn. A valid evaluation of its effect will depend upon a comparison of treated and untreated control subjects in whom hepatic coma has been precipitated by ingestion of exogenous ammonium salts. Inasmuch as hepatic coma of this type has not previously been differentiated from spontaneous coma, no such control data are now available.

SUMMARY

1. Blood ammonia concentrations have been studied in a series of thirty-one patients in forty-four episodes of hepatic coma. Blood ammonia elevation has been found in 90 per cent of these patients. The clinical course of coma has in general been reflected in the degree of ammonia elevation.

2. In a number of cases the appearance of hepatic coma did not coincide with elevation of blood ammonia. Occasionally, typical hepatic coma was accompanied by persistently normal blood ammonia concentrations, while in other instances a markedly elevated ammonia level was not accompanied by any neurologic deficit. The significance of these findings is discussed.

3. It is suggested that at least two types of hepatic coma may occur. The first is precipitated by administration of exogenous ammonium salt or protein, is invariably associated with high blood ammonium levels and responds promptly to glutamate therapy. This is pure ammonia intoxication. The second type of coma occurs spontaneously during progressive hepatic failure, usually but not invariably is accompanied by elevated peripheral blood ammonia concentrations, and seldom is benefited by glutamate therapy.

REFERENCES

1. Burchi, R. Prüfung der Leberfunktion durch Untersuchung der spontanen und provozierten Ammoniämie. *Kongr. Zentralbl. ges. inn Med.*, 47: 80, 1927.
2. Calvert, R. J., Smith, E. and Werren, J. P. The biochemistry and management of hepatic coma. A review and case report. *Gastroenterology*, 26: 650, 1954.
3. Carfagno, S. C. Hepatic coma. *New England J. Med.*, 249: 303, 1953.
4. Van Caulaert, C. and Deviller, C. Ammoniemie experimentale après ingestion de chlorure d'ammonium chez l'homme a l'état normal et pathologique. *Compt. rend. Soc. de biol.*, 111: 50, 1932.
5. Van Caulaert, C., Devilles, C. and Halff, M. Troubles provoques par l'ingestion de sels ammoniocaux chez l'homme atteint de cirrhosis de Laennec. *Comp. rend. Soc. de biol.*, 111: 739, 1932.
6. Van Caulaert, C., Devilles, C. and Halff, M. Contribution a l'étude des cirrhosis de Laennec toxieté de l'ammoniaque. *Presse méd.*, 41: 217, 1933.
7. Conway, E. J. Microdiffusion Analysis and Volumetric Error, 3rd. ed. London, 1950. Crosby, Lockwood & Son.
8. Eiseman, B., Lindeman, G. and Johnson, J. A chemical means for determining the patency of a portacaval shunt. Forum on Fundamental Surgical Problems. Springfield, Ill., 1954. Charles C Thomas.
9. Foley, J. M., Watson, C. W. and Adams, R. D. Significance of electroencephalographic changes in hepatic coma. *Tr. Am. Neurol. A.*, 75: 161, 1950.
10. Fuld, H. Über die diagnostische Verwertbarkeit von Ammoniak bestimmungen in Blut. *Klin. Wchnschr.*, 12: 1364, 1933.
11. Gabuzda, G. J., Phillips, G. B. and Davidson, C. S. Reversible toxic manifestations in patients with cirrhosis of the liver given cation-exchange-resins. *New England J. Med.*, 246: 124, 1952.
12. Giges, B., Dein, H. L., Sborov, V. M., Seligson, D. and Howard, J. M. Experimental hepatic coma. *Surg., Gynec. & Obst.*, 97: 763, 1955.
13. Kirk, E. Amino acid and ammonia metabolism in liver diseases. *Acta med. Scandinav.*, (supp.) 77: 1, 1936.
14. McDermott, W. V. and Adams, R. D. Episodic stupor associated with an Eck fistula in the human with particular reference to the metabolism of ammonia. *S. Clin. Investigation*, 33: 1, 1954.
15. McDermott, W. V., Adams, R. D. and Riddell, A. G. Ammonia metabolism in man. *Ann. Surg.*, 140, 1954.
16. Monguio, J. and Krause, F. Über die Bedeutung des NH_3-gehaltes des Blutes für die Beurteilung der

Lebersfunktion. Studien am normalen, lebergeschädigten und Eckschen Fistelhund. *Klin. Wchnschr.*, 13: 1142, 1934.

17. Phear, E. A., Sherlock, S. and Summerskill, W. H. J. Blood ammonium levels in liver disease and "hepatic coma." *Lancet*, 1: 836, 1955.
18. Phillips, G. B., Schwartz, R., Gabuzda, G. J. and Davidson, C. S. The syndrome of impending hepatic coma in patients with cirrhosis of the liver given certain nitrogenous substances. *New England J. Med.*, 247: 239, 1952.
19. Quastel, J. H. and Wheatley, A. H. M. Oxidation by the brain. *Biochem. J.*, 26: 725, 1932.
20. Rappaport, A. M., MacDonald, M. H. and Borowy, Z. J. Hepatic coma following ischemia of the liver. *Surg., Gynec. & Obst.*, 97: 1, 1953.
21. Riddell, A. G. and McDermott, W. V. Hepatic coma. *Lancet*, 2: 1263, 1954.
22. Riddell, A. G., Kopple, P. N. and McDermott, W. V. The etiology of "meat intoxication" in the Eck fistula dog. *Surgery*, 37: 1954.
23. Schwartz, R., Phillips, G. B., Gabuzda, G. J. and Davidson, C. S. Blood ammonia and electrolytes in hepatic coma. *J. Lab. & Clin. Med.*, 42: 499, 1953.
24. Seligson, D. and Hirahara, K. To be published.
25. Singh, I. D., Barclay, J. A. and Cooke, W. T. Blood ammonia levels in relation to hepatic coma and the administration of glutamic acid. *Lancet*, 1: 1004, 1954.
26. Traeger, H. S., Gabuzda, G. J., Ballou, A. W. and Davidson, C. S. Blood "ammonia" concentration in liver disease and liver coma. *Metabolism*, 3: 99, 1954.
27. Walshe, J. M. Observations on the symptomatology and pathogenesis of hepatic coma. *Quart. J. Med.*, 20: 1951, 421.
28. Walshe, J. M. The effect of glutamic acid on the coma of hepatic failure. *Lancet.*, 1: 1075, 1953.
29. Weil-Malherbe, H. Studies on brain metabolism. The metabolism of glutamic acid in brain. *Biochem. J.*, 30: 665, 1936.
30. Weil-Malherbe, H. Significance of glutamic acid for the metabolism of nervous tissue. *Physiol. Rev.*, 30: 549, 1950.
31. White, L. P., Phear, E. A., Summerskill, W. H. J., Sherlock, S. and Cole, M. Ammonium tolerance in liver disease: observations based on catheterization of the hepatic veins. *J. Clin. Investigation*, 34: 158, 1955.
32. Woodrow, C. E., Frooms, K. and Lawrence, I. H. Acute hepatic necrosis. Coma treated with sodium glutamate. *Lancet*, 2: 1290, 1953.

Reviews

Subacute Combined Degeneration of the Spinal Cord*

Current Concepts of the Disease Process. Value of Serum Vitamin B_{12} Determinations in Clarifying Some of the Common Clinical Problems

MAURICE VICTOR, M.D. *and* ARNOLD A. LEAR,† M.D.
Boston, Massachusetts *Hyattsville, Maryland*

SUBACUTE combined degeneration of the spinal cord, the neurologic component of pernicious anemia, remains a perplexing and challenging disease to both the internist and neurologist. The main problem concerns the failure to make an early diagnosis, especially if the initial symptoms are neurologic and anemia is not apparent. This is of more than academic interest because long-standing degenerative lesions of the central nervous system are largely irreversible, and the damage that results from a delay in diagnosis may be recalcitrant to therapy. Further, the clinical and pathologic picture of subacute combined degeneration of the spinal cord, although highly characteristic, cannot always be readily differentiated from other diseases which affect the posterior and lateral columns of the spinal cord. Still another perplexing question which is of theoretic interest concerns the relation between subacute combined degeneration of the cord and pernicious anemia, and the precise role of vitamin B_{12} deficiency in production of both the hematologic and neurologic lesions.

Our own studies have required that we examine many aspects of subacute combined degeneration, which we shall discuss in the following pages. In doing this we propose first to summarize current concepts of the disease; secondly, to state the more common clinical problems relating to subacute combined degeneration of the spinal cord; and finally, to draw attention to the microbiologic assay of vitamin B_{12} in the serum, and to illustrate its clinical application by the presentation of appropriate case histories.

CURRENT CONCEPTS OF THE DISEASE

Lichtheim[1] in 1887, followed by his pupil Minnich,[2] were the first to describe the spinal cord disease accompanying pernicious anemia. In the decade that followed a large number of papers appeared which clearly delineated the main clinical and pathologic attributes of the neurologic disease as we know them today.[3–11] The intimate relationship of the spinal cord disease to pernicious anemia, however, was debated for many years. The relationship was denied by some of the most authoritative English authors;[9,11,12] and only following the writings of Bramwell[13] and Woltmann,[14] who stressed the high statistical coincidence, and of Hurst and Bell[15,16] who emphasized that gastric achlorhydria was the invariable common denominator of both, was their unity fully appreciated.

Clinical Manifestations of Subacute Combined Degeneration of Cord. The publications mentioned, and several others,[17–19] inform us that symptoms of nervous system disease are present in a high proportion of patients with pernicious

* From the Neurological Service, Massachusetts General Hospital, and the Thorndike Memorial Laboratory, Second and Fourth Medical Service (Harvard), Boston City Hospital, and the Departments of Medicine and Neurology, Harvard Medical School, Boston, Massachusetts. This study was aided in part by a Research Grant (M 767) from the National Institutes of Health (The Institute of Neurological Disease and Blindness), Public Health Service.

† Fellow in the Medical Sciences administered by the National Research Council for the Lilly Research Laboratories.

anemia, varying from 75 to 89 per cent according to different authors.[17,19,20] In general, the neurologic symptoms and signs have a uniform mode of onset and progression. In practically all instances the patients first notice general weakness and paresthesias. Of the latter, tingling or "pins and needles" feelings are the most common, to be followed in frequency by a large variety of other peculiar sensations, often vaguely described, such as numbness, stiffness, deadness, tightness, feelings of heat or cold, formication and shooting pains. The paresthesias tend to be constant, to progress steadily, and to be the source of much distress. They are usually localized to the distal parts of all four limbs in a symmetric distribution. The lower extremities are as a rule involved before the upper ones. Less often vague aches and pains, girdle sensations, cramping of the calves and even more rarely, bladder and bowel disturbances are the initial complaints; or there may be a disorder of the special senses, such as diminution of the sense of smell, or very rarely of visual acuity, perversions of taste, or roaring or thumping noises in the ears. As the illness progresses stiffness and weakness of the limbs develop, especially of the legs, and this, combined with a defect in postural sensation, produces a weak unsteady gait and awkwardness of the limbs. These symptoms, if untreated, may progress, and in their more advanced state take the form of an ataxic paraplegia with variable degrees of spasticity and contracture.

Early in the course of the illness, when only paresthesias are present, there may be no objective signs. Later, the neurologic examination may indicate a disturbance of all parts of the nervous system but mainly of the posterior and lateral columns of the spinal cord. Of the signs of posterior column affection, loss of vibration sense is by far the most consistent; this is more pronounced in the legs than in the arms and frequently the loss of vibration sense extends over the trunk, leaving little doubt that the nervous disorder is located in the posterior columns of the cord and not in the spinal roots or peripheral nerves. Position sense is involved somewhat less frequently, and in rare instances may even be more or less intact despite impairment of vibration sense. Characteristically there is greater impairment of deep than of superficial or cutaneous sensation, but the latter is by no means always spared. Isolated instances of loss of pain, temperature and tactile sensation below a segmental level on the trunk do occur, implicating the spinothalamic tracts, but such a finding should always suggest the possibility of some other disease of the spinal cord. More commonly the defect of superficial sensation takes the form of a mild blunting of touch, pain and temperature sensation over the limbs in a distal distribution.

Examination of the motor system discloses loss of power, spasticity, changes in the tendon reflexes, clonus and extensor plantar responses. Except in the most advanced cases these signs are practically limited to the legs, their prominence depending on the degree of corticospinal involvement. At first the patellar reflexes are found to be diminished in activity as frequently as they are increased, and may even be absent; the Achilles reflexes are more frequently depressed than hyperactive. With treatment the absent or depressed reflexes may return to normal or even become hyperactive. The abnormality of gait is governed by the relative amount of damage to the posterior and lateral columns of the cord and may therefore be predominantly ataxic or spastic, usually both. The nervous system involvement in subacute combined degeneration is characteristically although not always symmetric. A definite asymmetry of motor or sensory findings maintained over a period of weeks or months should always cast doubt on the diagnosis of subacute combined degeneration of the spinal cord.

Mental signs are frequent, ranging from irritability, apathy, somnolence, suspiciousness and emotional instability, to a marked confusional or depressive psychosis, or intellectual deterioration. Signs of visual impairment are distinctly rare and, when present, take the form of centrocecal scotomas. If involvement of the optic nerve is severe, optic atrophy may occur.[21,22]

Neuropathologic Changes in Subacute Combined Degeneration of Spinal Cord and Brain. The clinical signs are readily explained by the pathologic lesions of the nervous system, which have a characteristic appearance and a regular distribution. The pathologic process takes the form of diffuse although uneven degeneration of the white matter. There are multiple foci of spongy degeneration, often in relationship to small blood vessels, and varying from 0.1 to 2.0 mm. in diameter. The myelin sheaths and the axis cylinders are both affected, the former perhaps earlier and to a greater extent than the latter. There is relatively little fibrous gliosis,

except in treated cases in which destructive cord lesions existed prior to adequate therapy. In early cases only the posterior columns are affected and in more advanced cases the lesions here appear older. The changes most often begin in the posterior columns of the thoracic cord.[18] It would appear that they spread from this region up and down the cord as well as forward into the lateral columns. The lesions are not limited to specific systems of fibers within the posterior and lateral funiculi but are scattered irregularly through the latter. The paresthesias, impairment of vibratory and position sense, ataxia and the Romberg sign are due to affection of posterior columns, and lesions here may also account for loss of tendon reflexes. Weakness, spasticity, increased tendon reflexes and Babinski signs depend on involvement of the pyramidal tracts in the lateral columns. The spinothalamic tract may be involved in the pathologic process, which explains the occasional clinical finding of loss of pain and temperature sensation at a segmental level on the trunk. In advanced forms of the disease similar pathologic changes may occur in the white matter of the brain. Patients who disclose such lesions at postmortem examination will have shown mental symptoms during life, although cerebral lesions are found only infrequently in the cases in which mental symptoms were prominent. Instances of degenerative lesions of the optic nerves have also been verified at necropsy.[21,23]

There is no unanimity of opinion regarding peripheral nerve lesions in pernicious anemia. The clinical evidence of peripheral nerve involvement[20] is stronger than the pathologic and the existence therefore of disease in the spinal roots and nerves is largely inferential. For example, no lesions were found[17] in the spinal cord of a person who during life had shown sensory symptoms, a discrepancy which could best be explained by attributing the symptoms to peripheral nerve changes. It has been suggested by some authorities that reversibility of neurologic signs is indicative of peripheral nerve involvement.[24,25] The distal and symmetric blunting to pain, touch and temperature that occurs in many cases is certainly a point in favor of peripheral nerve disease. The pathologic findings have been difficult to determine and the reports are not altogether convincing.[3–9,17] Hamilton and Nixon[17] report lesions in peripheral nerves but the descriptions and illustrations are not satisfactory. Greenfield and Carmichael,[26] by making counts of nerve fibers in cross sections of a digital nerve of the foot, have shown that there is a loss of myelin without corresponding loss of axis cylinders.

Aside from the characteristic laboratory findings of pernicious anemia, there are few laboratory tests that are specifically helpful in the diagnosis of the nervous system disorder. The spinal fluid is usually normal, although occasionally there may be a slight elevation of the protein content. There are reports[27,28] of an electroencephalographic abnormality consisting of a diffuse slow-wave activity in many cases of pernicious anemia. This bears no relation to the age of the patient, the severity of the anemia or the presence of neurologic symptoms. The authors of these reports conclude that the changes in the electroencephalogram are due to a specific defect in cerebral metabolism. Scheinberg,[29] who studied cases of pernicious anemia by the nitrous oxide method of Kety and Schmidt, has found a reduction of oxygen and glucose consumption, also independent of the severity of the anemia. These latter data have not been duplicated.[30]

Efficacy of Liver and Vitamin B_{12} in Subacute Combined Degeneration. Therapeutic experiments have yielded much information concerning the cause and mechanism of both hematologic and neurologic components of the disease. At first it was believed that the spinal cord and blood changes were due to separate deficiencies and for this reason treatment with liver extract was supplemented with crude liver. However, there is now sufficient evidence that the response to vitamin B_{12} alone is in all ways comparable to that from refined liver extract or crude liver,[31] and that all the symptoms are due to deficiency of vitamin B_{12}. It has been suggested that the equivalent of 1 μg. of parenterally administered vitamin B_{12} daily may be an adequate dosage in the treatment of subacute combined degeneration of the cord but in practice the amount prescribed is usually higher.[32]

With the introduction of liver therapy the prognosis in subacute combined degeneration of the cord was radically altered. This was not immediately apparent, and in the early days of liver therapy it was thought that spinal cord symptoms could actually develop during liver therapy or progress despite treatment.[25,33–35] Others[19,36] recognized that weakness and mental signs improved with liver therapy but they

supposed that this was the result of improvement in general health and of the anemia.

With further study of cases without anemia and the development and use of refined liver fractions the salutary effects of treatment on the nervous symptoms became obvious. The improvement in neurologic signs has been shown to be quite dramatic and complete when effective therapy is instituted early after the onset of symptoms.[36] In practically all instances at least partial improvement is effected, although in long-standing cases often the best that can be accomplished is arrest of progression. The factors influencing the response to liver therapy and the nature of the improvement have been most carefully studied by Ungley,[31] whose views may be summarized as follows: The most important factor influencing the response to treatment is the duration of the disease as measured by the duration of difficulty in walking. The greatest improvement occurs in those whose difficulty in walking is of less than three months' duration; and, conversely, the least improvement occurs in those with difficulty in walking of longer than two years' duration. Factors of little or no importance were age, sex, severity, arteriosclerosis, hypertension and the degree of anemia. Neurologic relapses during therapy are usually associated with infections and can be corrected by increasing the dose of liver extract or vitamin B_{12}. Ungley finds that all neurologic symptoms and signs may be improved; that extensor plantar responses are as responsive to treatment as paresthesias and loss of vibratory sense. The return of absent deep reflexes is commonly observed, although at times it may take longer than a year. Most improvement occurs during the first three to six months of therapy, and whatever neurologic disorder is present after six months is likely to be permanent.

Pathogenesis of Pernicious Anemia and Subacute Combined Degeneration. The development of our present-day ideas concerning the pathogenesis of pernicious anemia has recently been the subject of several comprehensive reviews.[38–41] The modern concept of pernicious anemia dates from 1926 when Minot and Murphy[36] demonstrated the efficacy of liver in the dietary treatment of the disease and thus offered the first convincing evidence that pernicious anemia, with its accompanying neurologic lesions, was due to a nutritional deficiency. In the years that followed, oral liver therapy was succeeded by parenteral treatment with purified liver extracts and in 1948 the component of liver specifically active in pernicious anemia, vitamin B_{12}, was isolated.[42–44] This red, cobalt-containing vitamin was shown effectively to correct the hematologic and neurologic disorders of pernicious anemia when administered in only microgram doses.[37,45–47]

Shortly after the discovery of liver therapy Castle[49] offered a hypothesis of the pathogenetic mechanism. He suggested that an essential material (extrinsic factor) from the diet interacted with a constituent of normal gastric juice (intrinsic factor) and gave rise to an active erythrocyte-maturing factor. He also conclusively demonstrated that it is precisely this lack of intrinsic factor in the meager gastric secretion that characterizes the patient with pernicious anemia.[50,51] The exact nature of the intrinsic factor of Castle has not yet been defined, although potent purified intrinsic factor concentrates derived from hog duodenal mucosa have been prepared.[52] On the other hand, the extrinsic factor is now known to be vitamin B_{12} and it appears to be identical with the erythrocyte-maturing factor derived from liver. With present knowledge then, Castle's theory has been modified only slightly and pernicious anemia is now regarded as a conditioned nutritional deficiency in which, owing to a lack of intrinsic factor, dietary vitamin B_{12} is not absorbed and is therefore not available for normal metabolism. The precise mechanism whereby intrinsic factor effects the transfer of vitamin B_{12} to the tissue remains obscure but most likely its function is to facilitate the absorption of vitamin B_{12} from the upper gastrointestinal tract.[54] Once within the body, vitamin B_{12} is freely transported in the serum[55] and is available for hematopoiesis and for maintenance of the integrity of the nervous system.

Other specific nutrients have been shown to be temporarily effective in correcting the hematologic defect in pernicious anemia. Of these folic acid and its metabolically active form, the citrovorum factor, have been most extensively studied.[56–59] Although it was immediately evident that the anemia responded to the administration of folic acid,[50] subsequent studies clearly indicated that it was not the extrinsic factor. But, what is most important, folic acid does not prevent the development nor does it arrest the progression of the neurologic disease in pernicious anemia.[61,62] In fact, it may accelerate the development of nervous system lesions.[63]

By inference from microbiologic investigation, and to some extent from clinical studies, it would seem that the role of vitamin B_{12} and folic acid in hematopoiesis is concerned with nucleoprotein synthesis. This explains the interchangeability of these two vitamins in hematopoiesis. Vilter et al.,[41] Jukes[64] and Nieweg et al.[65] have outlined the interrelationships of these substances. Nieweg et al.[65] have suggested that folic acid fails to maintain the integrity of the nervous system because it functions in desoxyribonucleic acid synthesis and is not concerned with ribonucleic acid formation, as is vitamin B_{12}. The apparently deleterious action of folic acid upon subacute combined degeneration is still a matter for speculation but may be due to a mass action effect accelerating development of absolute vitamin B_{12} depletion,[41] the result of altered kinetics of vitamin B_{12} utilization or storage, or simply to the creation of vitamin imbalance by treating only part of the existing deficiency state.[66]

CLINICAL PROBLEMS

Lack of Correlation Between Degree of Anemia and Severity of Subacute Combined Degeneration. Subacute combined degeneration of the spinal cord confronts the clinician with many problems, the most important of which is that of making an early diagnosis. Perhaps the main reason for these difficulties is the lack of parallelism between the hematologic and neurologic manifestations. It is estimated that symptoms referable to the nervous system may be the presenting complaint in as many as 25 per cent of instances.[67] Even when anemia is present there may be no correlation between the degree of anemia and the severity of the neurologic disease; the latter may be far advanced in the presence of only the most subtle changes in the blood. When neurologic signs develop first, the onset of anemia is usually not long delayed, although in exceptional cases the interval may be more than a year.[20] To wait for the development of overt hematologic signs in order to confirm the neurologic diagnosis is hazardous to say the least. Because reversibility of the neurologic signs depends mainly on their duration before the institution of effective therapy, any delay in starting treatment seriously jeopardizes the chances for complete recovery.

Progression of Neurologic Disease Despite Normal Hematopoiesis. Since the introduction of folic acid new clinical difficulties have arisen. Early observations concerning the maintenance of hematologic remission with folic acid disclosed the fact that subacute combined degeneration of the cord may develop or even worsen in patients receiving folic acid alone.[60,61,66,68–71] Under these circumstances, as pointed out by Conley[72] and others, the patient may present neurologic signs as the sole manifestation of pernicious anemia, the blood having been maintained at normal levels by small amounts of folic acid in multiple vitamin preparations. The danger to the patient is obvious for during the hematologic remissions, which may be maintained for an indefinite period, the neurologic signs may progress often to an irreversible stage.

Differential Diagnosis of Subacute Combined Degeneration. Neurologists may be faced with still another clinical problem. Patients in adult and late life may present with a clinical syndrome implicating the posterior and lateral columns of the spinal cord, or what is in effect a combined system disease. Aside from pernicious anemia, this syndrome, presenting as an ataxic paraparesis, may have a variety of causes, such as spinal cord compression of diverse etiology, cervical spondylosis, leutic meningomyelitis, non-specific arachnoiditis and multiple sclerosis. When these causes are excluded, however, a sizable number of patients still remains with intrinsic disease of the spinal cord, to be distinguished from combined system disease due to pernicious anemia. Usually the distinction can be made on clinical grounds alone. Thus in patients with a combined system disease not associated with pernicious anemia signs of lateral column disease may precede those of the posterior column, and may be more prominent throughout the illness; or the neurologic signs may have been present without evidence of anemia for several years, that is, for a longer period than is customary in pernicious anemia. The presence of free hydrochloric acid in the patient's gastric secretion will almost certainly settle the issue. On the other hand there are some cases of the non-pernicious anemia type of combined system disease that are indistinguishable from the type associated with pernicious anemia. The neurologic symptoms and signs are almost identical and the syndrome is of such recent origin that the absence of anemia cannot be used as a criterion for diagnosis. Nor is achlorhydria a specific criterion, for patients may lack free acid in the presence of intrinsic factor. Bloomfield and Polland[73]

found that 21 per cent of 203 "normal" persons over fifty years of age had achlorhydria, even after the injection of histamine.

Other clinical situations may also cause difficulty in diagnosis. These concern patients with macrocytic anemia due to folic acid deficiency or other causes whose associated neurologic complications may be mistaken for those of pernicious anemia. Thus a patient with macrocytic anemia may suffer from beriberi, Wernicke's encephalopathy, Korsakoff's psychosis or spinal spastic ataxia of nutritional origin; or from such unrelated disorders as diabetic neuropathy or tabes.

TABLE I
SERUM VITAMIN B_{12} CONCENTRATIONS

Group	Number of Subjects	Total Vitamin B_{12} Level ($\mu\mu$g./ml.)	
		Range	Mean
Normal	20	292–856	532 ± 161*
Pernicious anemia in relapse	33	0–85	39 ± 26
Pernicious anemia in remission	22	123–1,330	525 ± 337
Neurologic disease excluding subacute combined degeneration	14	195–760	439 ± 170
Achlorhydria excluding pernicious anemia	9	225–800	450 ± 234
Folic acid deficiency	12	148–557	307 ± 130
Hepatic cirrhosis	29	193–2,200	714 ± 534
Miscellaneous	40	115–1,029	.....

* Standard deviation.

VALUE OF SERUM VITAMIN B_{12} DETERMINATIONS

In these perplexing clinical problems we have found the estimation of serum vitamin B_{12} to be of considerable aid. The concentration of vitamin B_{12} in body fluids can be measured by microbiologic technic, employing an algal flagellate, Euglena gracilis.[74] The details of the method used and results obtained have been reported elsewhere.[75] Inasmuch as the growth response of this microorganism is directly proportional to the amount of vitamin B_{12} present, comparison of growth stimulated by serum samples with that produced by known amounts of vitamin B_{12} affords an estimate of the vitamin B_{12} content of specimens assayed. The serum content of vitamin B_{12} in a variety of conditions is shown in Table I.

The striking and consistent deviation of the levels in patients with pernicious anemia in relapse from those of normal subjects suggests that the finding of a low level is a highly reliable index of vitamin B_{12} deficiency. The serum vitamin B_{12} concentration is thought to reflect tissue content, and hence low serum levels may occur with or without hematologic and with or without neurologic aberrations. The practical value of such a vitamin assay will be evident from the following clinical examples.

CASE REPORTS

CASE 1. *A patient with hematologic signs of pernicious anemia had a complete remission with injections of liver extract. Eighteen months after changing to oral folic acid, subacute combined degeneration of the cord developed; the blood morphology remained normal. Initially the serum vitamin B_{12} level was low. It returned to normal following vitamin B_{12} injections and her neurologic signs improved.*

E. A. (No. 791730) a fifty-seven year old woman, was admitted to the Massachusetts General Hospital on November 5, 1952, complaining of tingling of the hands and feet of six months' duration, and difficulty in walking of two months' duration.

In January, 1945, she first complained of loss of appetite, soreness of the tongue, a "metallic taste," tingling of her hands and feet, exertional dyspnea and ankle edema. At that time her physician recorded the following: red blood cells 3,320,000 per cu. mm.; hemoglobin 70 per cent; white blood cells 6,350 per cu. mm. with polymorphonuclears 49 per cent, band forms 2 per cent, lymphocytes 44 per cent, eosinophils 5 per cent. The blood smear showed marked variation in the size and shape of the red corpuscles. A diagnosis of pernicious anemia was made and on February 1, 1945, treatment with liver extract was instituted. Her symptoms improved and by January, 1946, her red blood count was 5,050,000 per cu. mm., hemoglobin 100 per cent, and the blood smear was normal.

In April, 1950, the patient felt well and her blood count was still normal. Purified liver injections were discontinued, and capsules of rubrafolin,® two to four daily were substituted. In December, 1951, an ache developed in the arches of the feet, as well as mild tingling in the feet and hands. In April, 1952, these symptoms became worse, although a blood count at this time was reported as normal. Numbness and aching pain gradually became more intense, extending up to the thighs and eventually to the buttocks, groin and lower back. In August, 1952, the patient noticed difficulty in maintaining her balance and increasing irritability and forgetfulness. In late October, 1952, there was accelerated progression of her symptoms and she was able to walk only with assistance.

Examination revealed an obese woman who was easily fatigued and tearful. Blood pressure was 160/90, and otherwise her vital signs were normal. The tongue

* Each capsule contained vitamin B_{12} 25 μg., folic acid 1.67 mg.

was slightly reddened and depapillated. In the legs all muscles were slightly weak but of good bulk. Slight incoordination was noted on heel-to-shin testing. The gait was grossly ataxic; her feet were placed on a wide base, her steps were uneven in length, unpredictable, and she lurched from side to side. Romberg's sign was present. The tendon reflexes were symmetrically brisk in the arms but absent at the knees and ankles. The plantar response was extensor bilaterally. In the hands there was an impairment of vibratory sense but it was not certain that there was an alteration in any other sensory modality. Vibratory sensation (256 DV) was absent at the iliac crests and below. Position sense was greatly impaired or absent in the toes, and slightly reduced at the ankles. There was blunting to pain and touch below the knees, most prominent in the feet.

Examination of the blood (November 5, 1952) revealed: red blood cells 4,350,000 per cu. mm.; hemoglobin 13.0 gm. per cent; white blood cells 6,500 per cu. mm. with 72 per cent polymorphonuclears, 24 per cent lymphocytes, 2 per cent monocytes, 1 eosinophil, 1 basophil. The only abnormality to be seen in the blood smear was a slight variation in the size of the red corpuscles. A gastric analysis yielded no free acid after histamine.

Serum vitamin B_{12} content was less than 10 $\mu\mu$g. per ml. On November 7, 1952 intramuscular injections of vitamin B_{12} were started. Three months later the patient's gait was much steadier. Position sense was improved in the toes and there was only the slightest abnormality of touch and pain sensation in the feet. The vitamin B_{12} serum content at this time was 924 $\mu\mu$g. per ml.

CASE II. *This patient was treated for anemia with transfusions and liver injections. His medication was then changed to an oral vitamin preparation, and three years later, although his blood morphology remained normal, subacute combined degeneration of the cord developed. At this time the serum vitamin B_{12} level was 71 $\mu\mu$g. per ml. With vitamin B_{12} therapy his neurologic state improved.*

J. H. (No. 440638), a sixty-five year old carpenter, was admitted to the Massachusetts General Hospital on May 25, 1953, complaining of difficulty in walking. In March, 1949, there was insidious onset of gradually increasing generalized weakness, giddiness and tingling of the hands and feet. Blood examination at another hospital was reported as follows: red blood cells 2,520,000 per cu. mm.; hemoglobin 51 per cent; white blood cells 5,200 per cu. mm. with 52 per cent polymorphonuclears, 40 per cent lymphocytes, 8 per cent monocytes, 8 per cent eosinophils. The smear showed moderate variation in the size and shape of the red corpuscles. A diagnosis of "secondary anemia" was made. Four transfusions were given and the symptoms improved dramatically. The patient was then given liver injections (of undetermined amount and type) at weekly intervals for nine months. In January, 1950, the liver injections were discontinued and liafon®* capsules were substituted. With the exception of a three-month period in 1951 when the patient took becotin®† capsules, the liafon capsules were taken once daily, until April 15, 1953. For six weeks prior to the present admission to the hospital he took three capsules of perihemin®‡ daily.

The patient was asymptomatic until about mid-April, 1953, when he noticed "coldness, deadness and numbness" of the feet, and a tendency to stagger. These symptoms progressed and two weeks before hospital admission similar paresthesias developed in the fingers, and the patient required support to walk.

Examination on May 25, 1953, showed a well preserved, muscular, white haired man. Blood pressure was 104/60 and other vital signs were normal. His tongue was fissured but not sore or depapillated. Stance and gait were grossly abnormal. He stood with his legs set widely apart but even in this position there was considerable swaying; with his feet together he could not stand unsupported. The gait was markedly ataxic, his arms being held out at the sides to guard against falling, and as he walked he watched his feet closely. He showed a definite Romberg's sign. There was a mild decrease in strength generally but no spasticity. Reflexes were normally brisk and equal in the arms; the patellar reflexes were reduced and the Achilles reflexes were unobtainable even with reinforcement. The plantar response was clearly flexor on the right and probably so on the left. There was mild blunting to a light tuning fork (256 DV) in the fingers, diminution of tactile sensibility over the feet, loss of position sense in the toes, and loss of vibration sense to the level of the eleventh thoracic vertebral spine.

Blood studies prior to treatment revealed: red blood cells 4,500,000 per cu. mm.; hemoglobin 14.8 gm. per cent; hematocrit 47 per cent; mean corpuscular volume 104 cu. μ; mean corpuscular hemoglobin concentration 31 per cent; white blood cells 4,900 per cu. mm. with a normal differential count. A gastric analysis yielded no free acid after histamine. A smear of the sternal marrow was normal. Serum vitamin B_{12} level was 71 $\mu\mu$g. per ml.

As early as three weeks after the institution of treatment with vitamin B_{12} there was recession of the coldness in the legs and improvement in gait. Six months later only a mild degree of ataxia was evident on walking, and only slight swaying in the Romberg

* Each capsule contains ferrous sulfate 0.132 gm., ascorbic acid 50 mg., folic acid 1.67 mg., desiccated liver 0.5 gm.

† Each capsule contains thiamin 10 mg., riboflavin 10 mg., pyridoxine 5 mg., vitamin B_{12} 1 μg., nicotinamide 50 mg., pantothenic acid 25 mg., desiccated liver 0.39 mg.

‡ Ferrous sulfate 192 mg., folic acid 0.85 mg., vitamin B_{12} 10 μg., ascorbic acid 50 mg., extract of stomach powder 100 mg., extract of insoluble liver fraction 350 mg.

position; ankle jerks were still absent but the plantar responses were now clearly flexor. Position sense had returned in the toes to some degree and vibration sense was present everywhere, although blunted at the knees, ankles and toes.

Comment: There is a striking similarity between Cases I and II. In both there was a progressive evolution of a neurologic illness over a period in which there was little abnormality of the red cells. Also in both instances the original illness was probably pernicious anemia, and it was corrected by appropriate therapy. After liver therapy was abandoned small doses of folic acid maintained normal red cell morphology but did not prevent the development of neurologic lesions. In both cases the serum vitamin B_{12} level was very low, in the face of hematologic remission. With vitamin B_{12} therapy there was restoration of function: in case I it was incomplete, and after three months the patient was still severely handicapped. In case II there was considerable improvement in the neurologic signs, probably because of the relatively short duration of symptoms prior to the institution of therapy.

CASE III. *A patient with the early signs of subacute combined degeneration of the cord but without anemia was treated with multiple vitamins including folic acid. Neurologic signs progressed, and almost two years elapsed after the onset of symptoms before anemia developed and the neurologic diagnosis was made.*

T. J. S. (No. 787766), a sixty-five year old retired plumber, was admitted to the Massachusetts General Hospital on September 12, 1952, because of inability to walk of five weeks' duration.

In the summer of 1951 he noticed numbness and tingling of the hands and feet, a feeling of tightness and cramps in the calves, and difficulty in walking. These symptoms progressed steadily to a point where the patient lost the feeling in his hands and could no longer climb or descend stairs. For these reasons he was admitted to another hospital in December, 1951. History taken at that time also revealed that the patient was accustomed to drinking five to seven glasses of beer daily, although his diet was adequate. Examination revealed a moderately obese elderly man; blood pressure 150/80, other vital signs normal. There were multiple small telangiectasia over the trunk and arms. The right cornea was densely scarred, the result of childhood trauma. The tongue was papillated and of normal color. There was a mild degree of dorsal kyphosis and emphysematous configuration of the chest. The patient was alert and lucid. He had difficulty in getting up from a chair. He was unable to stand with his feet together, and he walked with considerable unsteadiness, his legs being closely watched and placed widely apart. There was a mild tremor of the outstretched hands. Muscle power was reduced in the hands and in the dorsiflexors of the feet. Tendon reflexes were sluggish but equal in the arms, and absent in the legs. The plantar response was flexor in the right and equivocal on the left. Position sense was slightly impaired in the fingers and lost in the toes. Vibration sense was lost in the legs and trunk up to the lower costal margin. There was blunting but not complete loss of tactile and painful sensibility over the legs, most marked distally.

Because pernicious anemia with subacute combined degeneration of the cord was suspected the peripheral blood was carefully examined. The hematocrit was 42 per cent on one occasion and 43 per cent on another; white blood cells 7,800 per cu. mm. with polymorphonuclears 64 per cent, lymphocytes 30 per cent, monocytes 5 per cent, eosinophils 1 per cent. The smear revealed no abnormalities. Bone marrow aspiration was not done. There was an achlorhydria even after histamine. Blood chemical studies and examination of stools and spinal fluid revealed no abnormalities.

A diagnosis of alcoholic polyneuropathy was made. The patient remained in the hospital for almost three weeks, with little change in his signs. He was then transferred to a convalescent hospital where he remained for three months and was then discharged. A multiple vitamin preparation* was prescribed in December, 1951, which he took faithfully, six tablets daily. A progressive increase in all his neurologic symptoms ensued, especially of the weakness and staggering, so that by August, 1952, he was confined to bed.

On September 12, 1952, he was admitted to the Massachusetts General Hospital. He was unable to stand without support. There was moderate weakness of all muscle groups in the legs, most marked in the dorsiflexors of the feet, and greater on the right side. There were occasional flexor spasms, more prominent in the right leg. The leg muscles were mildly atrophic and tender on deep pressure. No deep reflexes could be elicited but the plantar response was bilaterally extensor. Vibration sense was lost below the rib cage and diminished up to the second rib. It was absent also at the wrists and fingers, and diminished at the elbows. Position sense was lost at the ankles and fingers, and impaired at the knees. In the legs there was an impairment of tactile and pain sensation to a level just above the knees, more in the right leg.

There was an achlorhydria after histamine. The blood examination revealed: red blood cells 2,960,000 per cu. mm.; hemoglobin 9.5 gm. per cent; hematocrit 33 per cent; mean corpuscular volume 111 per cu. μ; mean corpuscular hemoglobin concentration 34 per cent; white blood cells 4,850 per cu. mm. with polymorphonuclears 78 per cent, lymphocytes 21 per cent, basophils 1 per cent. Reticulocyte count was 0.5 per cent. The smear showed definite macrocytosis,

* Cheney vitamins: vitamin A 5000 units, vitamin D 500 units, vitamin C 15 mg., vitamin B_1 2 mg., vitamin B_6 0.2 mg., vitamin B_{12} 1 μg., folic acid 0.25 mg., pantothenic acid 3.0 mg., niacin 3.0 mg., yeast concentrate 60 mg.

mild anisocytosis and poikilocytosis. The polymorphonuclear cells were large and multilobed. The aspirated sternal bone marrow showed megaloblastic erythropoiesis. The serum vitamin B_{12} level was 63 $\mu\mu$g. per ml.

A cystometrogram indicated a small bladder capacity with severe pain and voiding after the introduction of 300 cc. of fluid. Electrocardiograms showed a right bundle-branch block. The remainder of the laboratory examinations, including blood serologic tests, lumbar puncture, stool examinations, chest films, intravenous pyelograms and gastrointestinal series revealed no abnormalities.

On September 22, 1952, vitamin B_{12} therapy was instituted. Five months later his blood count was normal and he showed considerable neurologic improvement.

CASE IV. *For eight years this patient was treated for anemia with capsules containing liver, iron and multiple vitamins, and sporadic liver injections. Then oral medication was changed to include folic acid. This was followed by the development of neurologic signs and recurrence of the anemia, accompanied by an absence of vitamin B_{12} in the serum.*

G. F. (No. 838654), a fifty-three year old white woman, was admitted to the Massachusetts General Hospital on February 10, 1954, complaining of an inability to walk of several weeks' duration.

In 1943, the patient noted shortness of breath, tiredness and exhaustion, insomnia and nervousness. Her physician found her to be anemic: red blood cells 1,430,000 per cu. mm.; white blood cells 4,000 per cu. mm.; hemoglobin 50 per cent. For the next eight years she took capsules of extralin® B* (six daily), and multicebrin®† (once daily). Also over this period she received liver injections at very long and irregular intervals, and ate 3 to 4 ounces of liver daily. Her red cell values returned to normal and remained stable, and in June, 1951, her red blood count was 4,560,000 per cu. mm., and hemoglobin was 14.2 gm. per cent. In July, 1951, she discontinued her medication. Two months later her blood values were: red blood cells 3,170,000 per cu. mm.; hemoglobin 8.6 gm. per cent; hematocrit 29 per cent. For this reason she was given liafon‡ capsules, in a dosage of four daily. Several weeks later she first noticed a feeling of stiffness in the legs and coldness of her hands and feet. Her blood over the next few months returned to normal (red blood cells 4,140,000 per cu. mm.; hemoglobin 12.4 gm. per cent), although her legs continued to feel "stiff and like ice." Three weeks prior to admission there was a sudden deterioration of gait, accompanied with paresthesias of the hands and feet.

On physical examination pallor was obvious. The patient was unable to turn over in bed or to stand or to walk without help. All leg movements were feeble, especially flexion of the hip. The extensor muscles of the legs were somewhat spastic. The patellar and Achilles reflexes were hyperactive and there was ankle clonus and an extensor plantar response bilaterally. Position sense was lost in the toes and ankles, and vibration sense was lost below the level of the third lumbar vertebra. The bladder was distended and catheterization yielded a residual urine of 1,100 cc.

Blood examination on February 10, 1954, revealed: red blood cells 2,630,000 per cu. mm.; hemoglobin 10.2 gm. per cent; hematocrit 27 per cent; mean corpuscular volume 103 cu. μ; white blood cells 4,000 per cu. mm., with a normal differential count. The smear showed multisegmented large polymorphonuclear cells, frequent macrocytes, marked variation in size and shape of the red cells, moderate polychromatophilia, and an occasional nucleated red cell. The platelets appeared decreased in number. The reticulocyte count was 1.1 per cent. There was achlorhydria after histamine. The serum vitamin B_{12} level was less than 10 $\mu\mu$g. per ml.

Treatment with parenteral vitamin B_{12} was begun on February 12, 1954. On the sixth day the maximal reticulocyte response of 10.5 per cent was reached. There was a rapid improvement in general strength and sense of well-being. The bladder disturbance reverted to normal over a week's time with the aid of small doses of furmethide.®

Four weeks after the institution of therapy the red blood count was 4,090,000 per cu. mm. and the hemoglobin was 13.4 gm. per cent. Strength in the trunk and legs was greatly improved. The patient was able to stand and walk by herself, on a narrow base, with short, stiff, uncertain steps. Five months after therapy was started the patient walked briskly without support. There was only slight swaying and moderate spasticity of the legs. Motor power was excellent. Reflexes were unchanged. She was now able to perceive vibration at the iliac crests and knees, although it was still diminished. Position sense had improved slightly.

Comment: In many respects Cases III and IV are similar. Despite the evolution of a neurologic disorder, the nature of the condition was unrecognized because of the absence of anemia. The lack of parallelism in the evolution of the blood and nervous system disorder was present for at least six months in Case III. In both cases hematologic relapse was prevented for a long time by oral folic acid medication. Only after the neurologic damage had become far advanced did the anemia become prominent and the diagnosis evident. In both these cases folic acid failed to prevent not only a neurologic but also an eventual hematologic

* Each capsule contains: liver-stomach concentrate 0.6 gm., thiamine hydrochloride 0.15 mg. and riboflavin 0.07 mg.

† Vitamin A 10,000 U.S.P. units, vitamin D 1,000 U.S.P. units, thiamine hydrochloride 3 mg., riboflavin 3 mg., pyridoxine hydrochloride 1.5 mg., nicotinamide 25 mg., pantothenic acid 5 mg., ascorbic acid 75 mg., distilled natural tocopherols 10 mg.

‡ See footnote on p. 902.

relapse. A few points of difference in the two cases are worth noting. Although both suffered from bladder disturbance, it was of a spastic type in Case III and of an atonic type in Case IV. The degree of recovery of neurologic function was also quite different—again a reflection of the duration of the signs prior to vitamin B_{12} therapy.

In addition to the cases already described we have observed two others that fall into the same category in that folic acid therapy failed to halt the progression of neurologic disease. One of these was a seventy-three year old woman with virtually complete paralysis of the legs. She had been taking perihemin,* which masked her marrow and blood changes almost completely (hemoglobin 11.5 gm. per cent; hematocrit 36 per cent; mean corpuscular volume 94 cu. μ). She had achlorhydria after histamine and a serum vitamin B_{12} level of 35 $\mu\mu$g. per ml. The other patient was a sixty-three year old man who was given perihemin,* four capsules daily, because of mild staggering. Over the next three months there was progressive evolution of a severe degree of spastic ataxia. His blood was little altered, although megaloblasts were present in his bone marrow.

CASE V. *A patient with advanced subacute combined degeneration of the cord had only mild anemia, and a reduced serum vitamin B_{12} level.*

J. S., a sixty-eight year old man, was admitted to the Boston City Hospital on May 20, 1953, complaining of pain in his knees and difficulty in walking. A sequential history was difficult to obtain. He apparently had difficulty with his legs for several years, mainly pain in his knees and an inability to walk a long distance. On direct questioning he admitted to numbness and tingling of his hands and feet but their time of onset could not be ascertained. Apparently in the few months prior to admission there was rapid progression of his leg symptoms, leading to complete inability to walk. Gastrointestinal and urinary symptoms were denied, as were symptoms that might be attributable to anemia.

The patient was a pleasant elderly man; his blood pressure was 118/78, and other vital signs were normal. Although oriented in place he was uncertain how long he had been in the hospital and only vaguely remembered the events since his hospital admission. There was no serious defect in recalling recently presented material, however, and he did not confabulate. There was definite weakness of the extensors of the wrists and intrinsic hand muscles, but no spasticity. With his eyes closed the outstretched arms drifted and the fingers assumed unnatural postures. There was slight weakness of the dorsiflexors of the feet and, to a lesser extent, of the other leg muscles. He was unable to stand or walk without assistance and even in bed there was gross ataxia of the legs on attempted movements. With support on both sides he made an attempt to walk, lifting his feet high and throwing them forward or to the side unpredictably. Deep reflexes were normally brisk and equal in the arms, and absent in the legs. The plantar responses were bilaterally extensor. In the fingers, vibration and position sense were impaired and pain and touch only slightly blunted. Vibration sense was lost to the level of the second lumbar spinous process and position sense was lost in the toes.

Examination of the blood on May 20, 1953, revealed only a slight anemia: red blood cells 3,980,000 per cu. mm.; hemoglobin 11.7 gm. per cent; hematocrit 39 per cent; white blood cells 5,580 per cu. mm. with a normal differential. The smear showed only slight macrocytosis and anisocytosis. The red cell indices were: mean corpuscular volume 97 cu. μ; mean corpuscular hemoglobin concentration 30 per cent. On May 27, 1953, the serum vitamin B_{12} level was 20 $\mu\mu$g. per ml.

A second blood examination one week after admission revealed: red blood cells 3,380,000 per cu. mm.; hemoglobin 11.2 gm. per cent; hematocrit 33 per cent; mean corpuscular volume 98 cu. μ; mean corpuscular hemoglobin concentration 34 per cent. The sternal marrow aspirate contained numerous megaloblasts and giant metamyelocyte and platelet forms. There was an achlorhydria after histamine.

Following parenteral vitamin B_{12} therapy the blood count slowly returned to normal, the peak reticulocyte response being only 5 per cent. Ten weeks after admission there was practically no change in his neurologic status.

Comment: The patient's history was of little help in diagnosis but examination revealed evidence of severe affection of the posterior and lateral columns of the spinal cord. The achlorhydria was compatible with but not diagnostic of subacute combined degeneration of the cord. There was in this case, as in Case III, a lack of parallelism between the hematologic and neurologic signs—the latter being well entrenched and irreversible while the former were mild and perhaps only evolving. An additional point of interest was the pronounced megaloblastosis of the marrow despite a relatively mild degree of anemia, suggesting that megaloblastosis may be a function of the degree of vitamin B_{12} deficiency. Because of the megaloblastosis the serum vitamin B_{12} estimation was confirmatory rather than essential, although it might have been of crucial value at an earlier stage of the illness.

CASE VI. *A typical case of pernicious anemia, characterized by neurologic signs, a low serum vitamin B_{12}, and an inordinate delay in diagnosis.*

Mrs. C. P. (No. 632927), sixty-five years of age, was first seen in the neurologic outpatient department of the Massachusetts General Hospital in June, 1953, complaining of unsteadiness of gait. Her record revealed that on June 3, 1952, she was admitted to the hospital because of recurrent attacks of abdominal

* See footnote, p. 902.

pain, and on the next day her gallbladder was removed. Prior to the operation her hemoglobin was 11 gm. per cent and the white cell count was 8,000 per cu. mm. During the operation she was transfused with 500 cc. blood, and three days later, since her hemoglobin was only 9 gm. per cent, she received another 500 cc. of blood. On June 15th uncomfortable stomatitis and glossitis developed; the tongue was described as beefy red and atrophic, and this was attributed to penicillin. The patient was discharged to her home on June 18, 1952.

Following her discharge some soreness of the tongue remained. In addition she noted numbness and tingling in her feet. Several months later the same feeling spread to her hands, and at the same time she noted unsteadiness and staggering on walking. She fell on occasion, and required support to walk. In the last month before her admission to the hospital she could no longer use a knitting needle and noted cramps and soreness of the calves. She did not seek medical help for these symptoms, however, until May, 1953.

Examination revealed an alert, pleasant, somewhat deaf lady. Her tongue was red but not depapillated. She walked with feet slightly apart, and stumbled when she attempted to walk on a narrow base. There was mild weakness of the arms and legs at all joints, most prominent in the dorsiflexors of the feet. Deep reflexes were sluggish in the arms and absent at the knees and ankles. The plantar responses were equivocal. Vibration sense was not perceived at the iliac crests or below and was present but diminished in the fingers and wrists. Position sense was slightly impaired in the toes and fingers. There was blunting to pain and touch over both hands and in the legs up to about the mid-calf.

Her red cell count was: 2,780,000 per cu. mm.; hemoglobin 11 gm. per cent; hematocrit 34.5 per cent; mean corpuscular volume 124 cu. μ. The smear showed moderate macrocytosis and variation in size and slight polychromatophilia. Bone marrow aspirate revealed megaloblastic erythropoiesis, and gastric analysis showed no free acid even after histamine. The serum vitamin B_{12} level was 33 $\mu\mu$g. per ml.

After the onset of treatment with parenteral vitamin B_{12} the patient improved; she lost the mouth soreness and feelings of depression, and her hemoglobin returned to normal. The cramps and tenderness of the calves improved more slowly, while the parasthesias and the unsteadiness of gait gradually diminished over the period of a year. At the end of this time there was only slight uncertainty in walking. She could stand with feet together without swaying. Power was adequate. Position sense in the toes was now considered normal, and there was only blunting to a 128 DV tuning fork at the ankles and toes.

Comment: This case is presented as a typical instance of pernicious anemia, and as an example of the delay and negligence that is still encountered in diagnosis. In this case a year elapsed between the probable onset of pernicious anemia and institution of therapy. Originally, the anemia and gastrointestinal complaints failed to raise the suspicion of pernicious anemia, and were not adequately investigated. The glossitis and anemia were treated by discontinuing penicillin therapy and by blood transfusion, respectively. The patient then did not seek help for her paresthesias and disturbance of gait for nearly a year, over which period the nervous system was irreparably damaged.

CASE VII. *A patient with the subacute onset of symptoms of combined system disease was found to have normal blood values and gastric acidity, and a normal serum vitamin B_{12} content.*

Mrs. G. F. D. (No. 802727), fifty-two years old, was admitted to the Massachusetts General Hospital on February 20, 1953, with paralysis of the legs. She had been well until mid-December, 1952, at which time she noted the onset of progressive weakness and stiffness in her left leg, to be followed in about three weeks' time by the same symptoms in the other leg. Concomitant with the weakness there was numbness of the soles of her feet. In early January, 1953, she experienced numbness and tingling of the left hand, followed shortly by similar feelings on the right. The weakness in the legs progressed rapidly so that two weeks prior to admission she was unable to walk, and just before admission she was barely able to move her legs in bed. In the last two weeks there was some urinary urgency and frequency but no incontinence.

The general physical examination and the vital signs were normal. Blood pressure was 130/70. The paresthesias in the fingers were not accompanied by demonstrable sensory loss. The tendon reflexes in the arms were very active. There was almost complete paraplegia with spasticity and hyper-reflexia, clonus and Babinski signs. There was severe loss of position sense in the legs, and a loss of vibration sense up to the first lumbar vertebral spine. There was slight hypalgesia below the knees and in the sacral segments.

The gastric aspirate contained free acid. The blood values were: red blood cells 4,610,000 per cu. mm.; hemoglobin 14.2 gm. per cent; hematocrit 38 per cent; mean corpuscular volume 82 cu. μ; white blood cells 13,300 per cu. mm. with a normal differential. The smear appeared normal. Cerebrospinal fluid examination revealed no abnormalities. Myelography and x-ray films of the spine were similarly unrevealing. The serum vitamin B_{12} content was 367 $\mu\mu$g. per ml. The patient had received no medication aside from the hospital diet.

Comment: It was believed on the basis of the clinical and laboratory data, that cervical spondylosis, a compression lesion of the cord, luetic meningomyelitis and demyelinative disease were adequately excluded. It was concluded that the patient had a lesion of the posterior and lateral columns of the cord, most difficult to distinguish from those related to pernicious

anemia. The normal blood findings did not rule out the diagnosis of subacute combined degeneration of the cord but the finding of free acid on gastric aspiration rendered it highly unlikely. The serum vitamin B_{12} content was quite normal, despite the fact that this patient had received no vitamin B_{12} or liver therapy.

We have estimated the serum vitamin B_{12} level of four other similar patients. All of them had what was in effect a combined system disease, namely symptoms and signs of spinal cord disease involving the posterior and lateral columns. Similarly, they all had free acid on gastric aspiration. It is a point of interest that in all these patients the serum vitamin B_{12} content was normal, a feature which supports the contention that these cases of combined system disease represent an entity quite distinct from the cord disease of pernicious anemia. Furthermore, treatment with vitamin B_{12} or liver extract has not led to any significant change in their clinical status.

In this non-pernicious anemia form of combined system disease the determination of the serum vitamin B_{12} may have additional important diagnostic value. Such a circumstance arises in patients with gastric anacidity which is not associated with pernicious anemia but is the result of aging. The elderly patient with posterolateral column disease, without abnormalities of peripheral blood or bone marrow, and gastric anacidity presents a difficult problem in differential diagnosis which may be settled by estimating the vitamin B_{12} level in the serum. An example of such a case follows.

CASE VIII. *A patient with symptoms and signs of intrinsic spinal cord disease affecting the posterior and lateral columns. Blood findings were normal and he had gastric anacidity. The vitamin B_{12} content of the serum was normal.*

Mr. T. B. (No. 671051), age seventy-one, was first seen at the Massachusetts General Hospital on July 29, 1949, complaining of numbness and clumsiness of his fingers of more than two and a half years' duration, and a staggering gait of four weeks' duration. He also had symptoms of hesitancy, urgency and frequency of urination for an unspecified period of time.

Physical examination was normal excepting for an enlarged soft prostate and neurologic signs. The gait was ataxic, the legs being held stiffly and wide apart, and his steps short and uncertain. There was a slight generalized diminution in muscle power. Reflexes were hyperactive throughout, with Babinski signs and ankle clonus bilaterally. Tactile sensation was impaired in the hands. Vibration sense was absent at the elbows and below, and at the iliac crests and below. Position sense was impaired in the fingers and toes.

The blood values were: red blood cells 5,150,000 per cu. mm.; hemoglobin 15 gm. per cent; hematocrit 43 per cent; white blood cells 8,100 per cu. mm. The smear and differential count were normal. There was an achlorhydria after histamine. There was no abnormality of spinal fluid pressure, dynamics or constituents. X-ray films of the cervical spine showed only mild hypertrophic changes, and cervical myelography was normal.

For a three-year period, ending in December, 1952, the patient received purified liver extract parenterally in a dosage of 30 units weekly. There seemed to be only slight improvement in his gait as well as in his position and vibration sense over this period of time. One year after discontinuing liver therapy his neurologic symptoms and signs and his blood values were unchanged, and the serum vitamin B_{12} level was 360 $\mu\mu$g. per ml.

Comment: When first observed the clinical features of this man's illness were entirely consistent with those of subacute combined degeneration of the cord. The fact that the blood morphology was normal did not exclude the diagnosis, and the achlorhydria after histamine was compatible with pernicious anemia, or his age. With the exclusion of other causes of spinal cord disease (compressive lesions, luetic menigomyelitis and the like), subacute combined degeneration was still a diagnostic possibility. To settle this point two courses of action were open to the physician. One was to wait for hematologic signs to manifest themselves—a course usually considered too dangerous to pursue; the other—the one usually followed in such circumstances—was to commit the patient to liver therapy for an indefinite period, the diagnosis remaining in doubt. This patient failed to show any significant neurologic improvement after three years of liver therapy. The serum vitamin B_{12} content a year after cessation of liver therapy was normal. It is therefore unlikely that his cord disease was related to pernicious anemia. A serum vitamin B_{12} estimation at the outset of the illness could have settled this point.

We have observed another patient similar to the foregoing one, but more difficult diagnostically. In addition to the symptoms and signs of combined system disease and the achlorhydria after histamine, she was moderately anemic at the outset of her illness, although the anemia was not entirely characteristic of pernicious anemia: red blood cells 2,000,000 per cu. mm.; hemoglobin 8.2 gm. per cent; hematocrit 20 per cent; the peripheral blood smear showed some macrocytosis, anisocytosis, poikilocytosis. She was treated with intramuscular injections of liver (15 units weekly) but neither the anemia nor the neurologic signs improved. Two years after the cessation of liver therapy her serum vitamin B_{12} content was normal. Again, such a finding at the outset of the illness would greatly have clarified the clinical problem.

CASE IX. *A diagnosis of pernicious anemia and associated nervous system changes was made because of macrocytic anemia, megaloblastic marrow, achlorhydria, an ataxic gait and hypalgesia of the legs. A normal serum vitamin B_{12} content prompted re-evaluation of the case and resulted in a diagnosis of nutritional macrocytic anemia and Wernicke's encephalopathy.*

M. O'D. (No. 1511859), a thirty-four year old white woman, entered the Boston City Hospital on June 4, 1954, complaining of weakness and anorexia since January, 1953. The symptoms were steadily progressive and by February, 1954, she was spending most of the day in bed. Anorexia was severe, occasionally there was painless vomiting, weight loss and pallor were obvious, and in the few weeks prior to admission ankle edema developed. For many years there had been daily ingestion of about a pint of wine.

The patient weighed eighty-four pounds and showed a striking loss of muscle bulk, especially in the forearms and legs. Her face, hands, and especially her feet, were edematous. The tongue was red and the margins were depapillated.

The mental examination revealed no defects. There was a coarse horizontal nystagmus on lateral gaze to both sides. The patient walked on a wide base, with short uncertain steps, and required support to keep from falling. There was only slight reduction in muscle power, considering the loss of bulk. Tendon reflexes were brisk and the plantar responses were flexor. There was a mild degree of blunting to painful stimuli over the feet and lower legs.

Blood examination on June 4th revealed: red blood cells 1,400,000 per cu. mm.; hemoglobin 5.7 gm. per cent; hematocrit 17 per cent; mean corpuscular volume 121 cu. μ; mean corpuscular hemoglobin concentration 33 per cent; reticulocytes 3.3 per cent; white blood cells 5,700 per cu. mm.; differential count normal. The polymorphonuclear leukocytes were large and hypersegmented, the platelets were decreased in number, and macrocytosis, anisocytosis and poikilocytosis were evident. The bone marrow showed megaloblastic erythropoiesis. The gastric aspirate contained no free acid, even after the injection of histamine. Serum proteins were 5.1 gm. per cent, albumin 2.5, globulin 2.6 gm. per cent. A liver biopsy specimen revealed moderate amounts of hemosiderin in the liver cells, a slight increase in the connective tissue of the portal areas, and acute pericholangitis.

The patient was initially thought to have pernicious anemia with early nervous system changes. However, the serum vitamin B_{12} level was 360 $\mu\mu$g. per ml. and this prompted a re-evaluation of the diagnosis. The patient was given no specific therapy except the usual ward diet. By June 11th (seven days after admission) her reticulocytes had risen to 18.3 per cent; on this day a sternal marrow examination showed normoblastic erythropoesis. On June 14th peak reticulocytosis of 22.2 per cent was reached. On June 19th the gastric analysis was repeated and on this occasion a small amount of acid was detected after the injection of histamine. By July 13th the red blood count was 3,160,000; hemoglobin 11.4 gm. per cent; hematocrit 38 per cent; mean corpuscular volume 120 cu. μ; mean corpuscular hemoglobin concentration 30 per cent.

Comment: In this case the vitamin B_{12} determination was of critical diagnostic importance. Because the value was normal the gastric analysis was repeated and liver therapy was withheld. The presence of free gastric acid, the striking reticulocytosis with house diet alone and the normal serum vitamin B_{12} level suggest that the patient was suffering from folic acid deficiency. The neurologic signs, namely the nystagmus, ataxia of stance and gait, and mild distal blunting to pain sensation in the legs, were consistent with a mild form of Wernicke's encephalopathy and polyneuropathy, also on a nutritional basis.

DISCUSSION

The estimation of the vitamin B_{12} content of the serum affords an additional and refined aid in the diagnosis of subacute combined degeneration of the cord. The standard clinical and laboratory diagnostic methods have obvious shortcomings. Estimation of the gastric acidity is of limited value—if acid is present the diagnosis of subacute combined degeneration is unlikely. Blood and bone marrow examinations are most helpful, but only when they are abnormal. Where the diagnosis is in doubt, a therapeutic trial of vitamin B_{12} may be employed; recourse to such a procedure often means that therapy must be continued indefinitely, and that the diagnosis may remain in doubt unless additional studies are undertaken. In most instances the diagnosis of subacute combined degeneration of the cord can be made by utilizing the standard methods already described; in others, the diagnosis cannot be made with absolute certainty. Such occasions arise when the anemia is mild or absent or when the anemia has been corrected by folic acid therapy. On such occasions the serum vitamin B_{12} level may be of critical importance.

The vitamin B_{12} assay may be of further service to the neurologist, especially in distinguishing between the cord disease of pernicious anemia and that unassociated with pernicious anemia. In the former the vitamin B_{12} content is consistently low, providing that the patient has received no injections of liver or vitamin B_{12}, and in the latter it is normal. The finding of a normal serum vitamin B_{12} content in a patient with posterior and lateral column disease, especially if no free acid is present, provides convincing evidence that this form of neurologic disorder is not of the type which occurs as part of pernicious anemia.

Finally, vitamin B_{12} assay may be of practical diagnostic value in separating a wide variety of macrocytic anemias and neurologic disorders

from pernicious anemia and its neurologic symptoms.

A number of critical comments regarding the diagnosis and therapy of subacute combined degeneration of the cord can justifiably be made on the basis of the cases presented. It is a discouraging fact that in three of our patients (Cases II, IV and VI), who were anemic when first seen, examination of the blood was inadequate. It is entirely likely that the diagnosis of pernicious anemia could have been made in these patients at the outset of their illness had blood and bone marrow examination been complete. Since the damage to the nervous system represents a more pernicious aspect of this disease than does the anemia, thorough scrutiny of the blood is of special importance in patients who present themselves with neurologic symptoms (Cases I and II). When the peripheral blood is grossly normal and the neurologic signs predominate (Case III), the more subtle blood changes such as mild macrocytosis and the presence of large and multilobed polymorphonuclear granulocytes in the blood and marrow smears should be sought.

It is evident from our case histories that the necessity of proper and continued treatment of pernicious anemia was not fully appreciated. Thus in Cases I and II parenteral liver therapy was abandoned and oral vitamins were substituted, while in Cases III and IV the therapy consisted of oral vitamin preparations from the onset of the illness.

The practice of prescribing oral multiple vitamin preparations for patients with anemia, and more specifically of administering folic acid in the presence of vitamin B_{12} deficiency cannot be too strongly condemned. The dangers of such practices are well illustrated by our Cases I to IV inclusive, as well as in two other patients whose histories were not quoted in detail. In all these patients, despite the hematologic remission, neurologic signs developed which were to a large extent irreversible. Although this clinical phenomenon has been well substantiated and publicized in recent years,[60,61,66,68–72,76–80] we encountered six instances in the space of two years.

SUMMARY

Subacute combined degeneration of the spinal cord still poses many clinical problems, chiefly concerned with making an early diagnosis. The main reason for this difficulty is the lack of parallelism between the hematologic and neurologic manifestations. With the widespread administration of folic acid this problem has become more acute, since this drug may cause a hematologic remission for an indefinite period, while the neurologic signs worsen, often to an irreversible stage. Other problems concern the difficulty of distinguishing between intrinsic spinal cord disease of non-pernicious anemia type from combined system disease due to pernicious anemia; and of distinguishing pernicious anemia and subacute combined degeneration from other macrocytic anemias and their associated neurologic disturbances.

In all these difficult clinical problems the estimation of vitamin B_{12} in the serum affords a refined diagnostic method. A low serum B_{12} level is a reliable index of B_{12} deficiency, and may occur with or without hematologic and/or neurologic aberrations. It is particularly useful in the diagnosis of subacute combined degeneration of the cord when the anemia is mild or absent or when the anemia has been corrected by folic acid therapy.

The practice of prescribing oral multiple vitamin preparations for patients with anemia, and more specifically of administering folic acid in the presence of vitamin B_{12} deficiency, cannot be too strongly condemned.

Acknowledgments: The authors would like to thank Drs. Raymond D. Adams and William B. Castle for their suggestions and editorial help in the preparation of this article.

REFERENCES

1. Lichtheim. Zur Kenntniss der perniciösen Anämie. *Verhandl. d. Kong. f. inn. Med.*, 6: 84, 1887.
2. Minnich, W. Zur Kenntniss der im Verlauf der perniciösen Anämie beobachteten spinal Erkrankungen. *Deutsche Zeit. f. clin. Med.*, 21: 25, 264, 1893; 22: 60, 1893.
3. Van Noorden, C. Untersuchung über schwere Anämien. *Charité Annalen*, p. 217. Berlin, 1891.
4. Eisenlohr. Über primäre Atrophie der Magen- und Darmschleimhaut und deren Beziehung zu schwerer Anämie und Rückenmarkserkrankung. *Deutsche med. Wchnschr.*, 49: 1105, 1892.
5. Nonne, N. Beiträge zur Kenntniss der im Verlaufe der perniciösen Anämie beobachteten Spinalerkrankungen. *Arch. f. Psychiat.*, 25: 421, 1893.
6. Putnam, J. J. A group of cases of system sclerosis of the spinal cord, associated with diffuse collateral degeneration; occurring in enfeebled persons past middle life, and especially in women; studied with particular reference to etiology. *J. Nerv. & Ment. Dis.*, 16: 69, 1891.
7. Bowman, H. M. On the association of diseases of the spinal cord with pernicious anemia. *Brain*, 17: 198, 1894.

8. Russel, J. S. R. The relationship of some forms of combined degenerations of the spinal cord to one another and to anemia. *Lancet*, 2: 4, 1898.
9. Russel, J. S. R., Batten, F. F. and Collier, J. Subacute combined degeneration of the spinal cord. *Brain*, 23: 39, 1900.
10. Taylor, J. On nervous symptoms and morbid changes in the spinal cord. *Med. Chir. Tr.*, 78: 151, 1895.
11. Clarke, J. M. On the spinal cord degenerations in anemia. *Brain*, 28: 441, 1904.
12. Collier, J. In: Albutt and Rolleston's System of Medicine, vol. 7, p. 786. London, 1910. The Macmillan Co.
13. Bramwell, B. On the association of pernicious anemia with subacute combined degeneration of the cord. *Edinburgh M. J.*, 14: 260, 1915.
14. Woltmann, H. W. The nervous symptoms in pernicious anemia. *Collect. Papers Mayo Clin. & Mayo Found.*, p. 933, 1918.
15. Hurst, A. F. and Bell, J. R. The pathogenesis of subacute combined degeneration of the spinal cord, with special reference to its connection with Addison's (pernicious) anemia, achlorhydria and intestinal infection. *Brain*, 45: 266, 1922.
16. Ibid, *Brain*, 48: 218, 1925.
17. Hamilton, A. S. and Nixon, C. E. Sensory changes in the subacute combined degeneration of pernicious anemia. *Arch. Neurol. & Psychiat.*, 6: 1, 1921.
18. Greenfield, J. G. and O'Flynn, E. Subacute combined degeneration and pernicious anemia. *Lancet*, 2: 62, 1933.
19. Goldhamer, S. M., Bethell, F. H., Isaacs, R. and Sturgis, C. C. The occurrence and treatment of neurologic changes in pernicious anemia. *J. A. M. A.*, 103: 1663, 1934.
20. Woltman, H. W. The nervous symptoms in pernicious anemia; an analysis of one hundred and fifty cases. *Am. J. M. Sc.*, 157: 400, 1919.
21. Benham, G. H. H. The visual field defects in subacute combined degeneration of the spinal cord. *J. Neurol., Neurosurg. & Psychiat.*, 14: 40, 1951.
22. Hyland, H. H. and Sharpe, V. J. H. Optic nerve degeneration in pernicious anemia. *Canad. M. A. J.*, 67: 660, 1952.
23. Adams, R. D. and Kubik, C. S. Subacute degeneration of the brain in pernicious anemia. *New England J. Med.*, 231: 2, 1944.
24. Rundles, R. W. Prognosis in the neurologic manifestations of pernicious anemia. *Blood*, 1: 209, 1946.
25. Grinker, R. R. and Kandel, E. Pernicious anemia, results of treatment of the neurologic complications. *Arch. Int. Med.*, 54: 851, 1934.
26. Greenfield, J. G. and Carmichael, E. A. The peripheral nerves in cases of subacute combined degeneration of the cord. *Brain*, 58: 483, 1935.
27. Samson, D. C., Swisher, S. N., Christian, R. M. and Engel, G. L. Cerebral metabolic disturbance and delirium in pernicious anemia; clinical and electroencephalographic studies. *Arch. Int. Med.*, 90: 4, 1952.
28. Walton, J. N., Kiloh, L. G., Osselton, J. W. and Farrall, J. The electroencephalogram in pernicious anemia and subacute combined degeneration of the cord. *E. E. G. Clin. Neurophysiol.*, 6: 45, 1954
29. Scheinberg, P. Cerebral blood flow and metabolism in pernicious anemia. *Blood*, 6: 213, 1951.
30. Robin, E. D. and Gardner, F. H. Cerebral metabolism and hemodynamics in pernicious anemia. *J. Clin. Investigation*, 32: 598, 1953.
31. Ungley, C. C. Subacute combined degeneration of the cord. *Brain*, 72: 382, 1949.
32. Conley, C. L., Green, T. W., Hartmann, R. C. and Krevans, J. R. Prolonged treatment of pernicious anemia with vitamin B_{12}. *Am. J. Med.*, 13: 284, 1952.
33. Cohen, A. E. Subacute combined sclerosis progressive during remission of pernicious anemia. *J. A M. A.*, 90: 1787, 1928.
34. Sturgis, C. C., Isaacs, R. and Smith, M. Limitations of the liver treatment in pernicious anemia. *Tr. A. Am. Physicians*, 43: 127, 1928.
35. McAlpine, D. A review of the nervous and mental aspects of pernicious anemia. *Lancet*, 2: 643, 1929.
36. Minot, G. R. and Murphy, W. P. Treatment of pernicious anemia by a special diet. *J. A. M. A.*, 87: 470, 1926.
37. Berk, L., Denny-Brown, D., Finland, M. and Castle, W. B. Effectiveness of vitamin B_{12} in combined system disease. *New England J. Med.*, 239: 328, 1948.
38. Castle, W. B. Development of knowledge concerning the gastric intrinsic factor and its relation to pernicious anemia. *New England J. M.*, 249: 603, 1953.
39. Lester-Smith, E. Vitamin B_{12}. Part I. *Nutrition Abst. & Rev.*, 20: 795, 1951.
40. Ungley, C. C. Vitamin B_{12}. Part II. *Nutrition Abst. & Rev.*, 21: 1, 1951.
41. Vilter, R. W., Horrigan, D., Mueller, J. F., Jarrold, I., Vilter, C. F., Hawkins, V. and Seaman, A. Studies on the relationship of vitamin B_{12}, folic acid, thymine, uracil, and methyl group donors in persons with pernicious anemia and related megaloblastic anemias. *Blood*, 5: 695, 1950.
42. Lester-Smith, E. Purification of anti-pernicious anemia factor from liver. *Nature, London*, 161: 638, 1948.
43. Shorb, M. S. Activity of vitamin B_{12} for growth of Lactobacillus lactis. *Science*, 107: 397, 1948.
44. Rickes, E. J., Brink, N. G., Koninszy, F. R., Wood, T. R. and Folkers, K. Crystalline vitamin B_{12}. *Science*, 107: 396, 1948.
45. West, R. Activity of vitamin B_{12} in Addisonian pernicious anemia. *Science*, 107 : 398, 1948.
46. Bethell, F. H., Meyers, M. C. and Neligh, R. B. Vitamin B_{12} in pernicious anemia and puerperal macrocytic anemia. *J. Lab. & Clin. Med.*, 33: 1477, 1948.
47. Hall, B. E. and Campbell, D. C. Vitamin B_{12} therapy in pernicious anemia; effect on hematopoietic system; preliminary report. *Proc. Staff. Meet., Mayo Clin.*, 23: 584, 1948.
48. Hall, B. E. and Campbell, D. C. Vitamin B_{12} therapy in pernicious anemia; effect on general clinical and neurologic manifestations; preliminary report. *Proc. Staff Meet., Mayo Clin.*, 23: 591, 1948.
49. Castle, W. B. Observations on the etiologic relationships of achylia gastrica to pernicious anemia. I. The effect of the administration to patients with pernicious anemia of the contents of the normal

human stomach recovered after the ingestion of beef muscle. *Am. J. M. Sc.*, 178: 748, 1929.

50. Castle, W. B. and Townsend, W. C. Observations on the etiologic relationships of achylia gastrica to pernicious anemia. II. The effect of the administration to patients with pernicious anemia of beef muscle after incubation with normal human gastric juice. *Am. J. M. Sc.*, 178: 764, 1929.
51. Castle, W. B., Townsend, W. C. and Heath, C. W. Observations on the etiologic relationship of achylia gastrica to pernicious anemia. III. The nature of the reaction between normal human gastric juice and beef muscle leading to clinical improvement and increased blood formation similar to the effect of liver feeding. *Am. J. M. Sc.*, 180: 305, 1930.
52. Latner, A. L., Merrills, R. J. and Raine, L. C. Isolation of Castle's intrinsic factor. *Lancet*, 266: 497, 1954.
53. Berk, L., Castle, W. B., Welch, A. D., Heinle, R. W., Anker, R. and Epstein, M. Observations on the etiologic relationship of achylia gastrica to pernicious anemia. X. Activity of vitamin B_{12} as food (extrinsic) factor. *New England J. Med.*, 239: 911, 1948.
54. Wallerstein, R. O., Harris, J. W., Schilling, R. F. and Castle, W. B. Observations on the etiologic relationship of achylia gastrica to pernicious anemia. XV. Hematopoietic effects of simultaneous intravenous and of simultaneous or serial administration of intrinsic factor and vitamin B_{12}. *J. Lab. & Clin. Med.*, 41: 363, 1953.
55. Pitney, W. R., Beard, M. F. and Van Loon, E. J. Observations on the bound form of vitamin B_{12} in human serum. *J. Biol. Chem.*, 207: 143, 1954.
56. Jarrold, T., Horrigan, D., Thompson, C. and Vilter, R. W. Hamatologic effect of folinic acid (citrovorum factor) in persons with pernicious anemia. *Science*, 113: 688, 1951.
57. Ellison, R. R., Wolfe, S., Lichtman, H., Ginsberg, V. and Watson, J. Effect of citrovorum factor in pernicious anemia. *Proc. Soc. Exper. Biol. & Med.*, 76: 366, 1951.
58. Moore, C. V., Bierbaum, O. S., Welch, A. D. and Wright, L. D. Activity of synthetic lactobacillus casei factor (folic acid) as anti-pernicious anemia substance. Observations on two patients with Addisonian pernicious anemia and one with nontropical sprue. *J. Lab. & Clin. Med.*, 30: 1056, 1945.
59. Spies, T. D., Vilter, C. F., Koch, M. B. and Caldwell, M. H. Observations on the anti-anemic properties of synthetic folic acid. *South. M. J.*, 38: 707, 1945.
60. Heinle, R. W. and Welch, A. D. Folic acid in pernicious anemia. *J. A. M. A.*, 133: 739, 1947.
61. Vilter, C. F., Vilter, R. W. and Spies, T. D. The treatment of pernicious anemia with synthetic folic acid. 1. Observations on the maintenance of a normal hematological status and on the occurrence of combined system disease at the end of one year. *J. Lab. & Clin. Med.*, 32: 262, 1947.
62. Bethell, F. H. and Sturgis, C. C. Relation of therapy in pernicious anemia to changes in the nervous system. Early and late results in series of cases observed for periods of not less than 10 years and early results of treatment with folic acid. *Blood*, 3: 57, 1948.
63. Vilter, R. W., Vilter, C. F. and Hawkins, V. Combined system disease and hematologic relapse occurring in persons with pernicious anemia treated with synthetic folic acid (pteroyl glutamic acid) for a period of two years. *J. Lab. & Clin. Med.*, 32: 1426, 1947.
64. Jukes, T. H. Folic acid and vitamin B_{12} in the physiology of vertebrates. *Federation Proc.*, 12: 633, 1953.
65. Nieweg, H. O., Faber, J. G., de Vries, J. A. and Steufert Kwese, W. F. The relationship of vitamin B_{12} and folic acid in megaloblastic anemias. *J. Lab. & Clin. Med.*, 44: 118, 1954.
66. Davidson, L. S. P. and Girdwood, R. H. The imbalance of vitamins with particular reference to folic acid. *Lancet*, 1: 360, 1948.
67. Wintrobe, M. M. Clinical hematology, 3rd ed. Philadelphia, 1952. Lea & Febiger.
68. Ross, J. F., Belding, H. and Paegel, B. L. The development and progression of subacute combined degeneration of the spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic (folic) acid. *Blood*, 3: 68, 1947.
69. Israels, M. C. G. and Wilkinson, J. F. Risk of neurologic complications in pernicious anemia treated with folic acid. *Brit. M. J.*, 2: 1072, 1949.
70. Meyer, L. M. Folic acid in the treatment of pernicious anemia. *Blood*, 2: 50, 1947.
71. Wagley, P. F. Neurologic disturbances with folic acid therapy. *New England J. Med.*, 238: 11, 1948.
72. Conley, C. L. and Krevans, J. R. Development of neurologic manifestations of pernicious anemia during multivitamin therapy. *New England J. Med.*, 245: 529, 1951.
73. Bloomfield, A. L. and Polland, W. S. Gastric Anacidity. Its Relations to Disease. New York, 1933. The Macmillan Co.
74. Ross, G. I. M. Vitamin B_{12} assay in body fluids using Euglena gracilis. *J. Clin. Path.*, 5: 250, 1952.
75. Lear, A. A., Harris, J. W., Castle, W. B. and Fleming, E. M. The vitamin B_{12} concentration in pernicious anemia. *J. Lab. & Clin. Med.*, 44: 715, 1954.
76. Editorial. *Lancet*, 1: 182, 1947.
77. Editorial. *Lancet*, 1: 371, 1948.
78. Editorial. *New England J. Med.*, 237: 1947.
79. Chodos, R. B. and Ross, J. F. The effects of combined folic acid and liver extract therapy. *Blood*, 6: 1213, 1951.
80. Wintrobe, M. M. Shotgun anti-anemic therapy. *Am. J. Med.*, 15: 141, 1953.

The Treatment of Barbiturate Poisoning with or without Analeptics*

JAMES E. ECKENHOFF, M.D. *and* WILLY DAM, M.D.
Philadelphia, Pennsylvania *Copenhagen, Denmark*

THREE times during the past twenty years the Council on Pharmacy and Chemistry of the American Medical Association has deemed it of sufficient importance to report on the use of analeptic drugs in the treatment of barbiturate poisoning.[1–3] On all three occasions the lack of clinical proof of the effectiveness of analeptics was stressed. Since the last report, additional evidence concerning the treatment of barbiturate poisoning has appeared. The purpose of this presentation is to summarize and evaluate such evidence. It will be shown that the mortality from barbiturate poisoning treated by supportive therapy alone is strikingly low. It is apparent that metrazol,® picrotoxin and other analeptics do not increase the survival rate from barbiturate narcosis. The data imply that analeptics may even increase the death rate.

An important recent contribution to the problem of therapy of barbiturate poisoning has been the organization of a Center in Copenhagen, Denmark, for the treatment of poisoning. All comatose patients from Copenhagen and environs are taken to this Center. Admissions total about 900 patients yearly; 75 per cent are for barbiturate poisoning, 5 per cent for opiate poisoning, and in 6 per cent the etiologic agent producing coma is unknown. The remainder suffer from coma arising from miscellaneous conditions. This Center constitutes an excellent source for the accumulation of data concerning narcotic poisoning. One of the authors has been associated with the Center since its inception, while the other, during a recent visit, has been able to inspect case material, methods of therapy and results of treatment. In America, treatment in this Center as reported by Nilsson[4] has received considerable attention.[5] Other reports from the Copenhagen Clinic have appeared.[6–8]

COMPARISON OF DATA: SUPPORTIVE THERAPY ALONE VERSUS SUPPORTIVE THERAPY COMBINED WITH ANALEPTICS

Table I lists the mortality figures from groups advocating only supportive measures and Table II cites the figures from groups advocating the use of analeptics in addition to supportive therapy. Adequate supportive therapy alone has the lowest reported death rate.

TABLE I
MORTALITY IN BARBITURATE POISONING TREATED BY SUPPORTIVE THERAPY

Author or Clinic	Cases	Deaths	Mortality (%)
Nilsson[4] (1951)	176	3	1.7
Locket, Angus[9] (1952)	84	2	2.4
Copenhagen Center[10] (1950)	558	36	6.4
Copenhagen Center[10] (1951)	621	19	3.1
Totals	1439	60	4.2 (average)

The principles of supportive therapy can be outlined as follows:

Respiration. A patent airway must be maintained by prevention of soft tissue obstruction and meticulous removal of secretions from the pharynx and tracheobronchial tree. When pharyngeal and laryngeal reflexes are diminished or absent, the trachea should be intubated with an endotracheal tube (No. 35 French in adults, and smaller as indicated). This facilitates aeration and removal of secretions; a catheter for aspirating secretions should be passed through the endotracheal tube at least every hour, and the tube changed every twelve hours. The tube is removed when pharyngeal and tracheal reflexes and muscular tone return. Vocal cord granulomas may occur following prolonged tracheal

* From the Department of Anesthesiology, Hospital of the University of Pennsylvania and the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine; Department of Anesthesiology, Bispebjerg Hospital, Copenhagen, Denmark.

TABLE II

MORTALITY IN BARBITURATE POISONING TREATED BY SUPPORTIVE THERAPY AND ANALEPTICS

Author	Cases	Deaths	Mortality (%)	Analeptic
	61	27	44.0	Nikethamide
Riishede[11] (1950)	132	12	9.0	Amphetamine
Watts, Ruthberg[12] (1948)	58	6	10.3	Nikethamide
Jones et al.[13] (1950)	29	3	10.3	Metrazol Picrotoxin
Reed et al.[14] (1952): Part I	209	28	13.4	Picrotoxin Amphetamine Caffeine
Part II	91	5	5.5	
Totals	580	81	14.0 (average)	

intubation;[5] therefore, tracheotomy should be considered if intubation is required longer than three days.

Respiratory tidal exchange and minute volume must be adequate. The tidal exchange should exceed 350 cc. This can be estimated by careful observation or can actually be measured. Apnea, shallow respiration, duskiness of the skin, finger nails and lips, or hypercapnia as shown by the CO_2 blood content indicate the need for artificial respiration. A mechanical resuscitator, Drinker respirator or manual rhythmic compression of an anesthetic bag filled with oxygen will suffice for this purpose. During coma from any cause oxygen should be administered by mask or by a nasopharyngeal catheter delivering a flow of 6 L. per minute. If an endotracheal tube has been inserted, the flow should be 4 L. per minute.

To facilitate pulmonary ventilation and the drainage of secretions from the trachea and pharynx, the lateral decubitus position is optimal, with the head slightly lower than the feet. The patient should be turned hourly. Lowering the head end of the bed more than five degrees may interfere with respiratory exchange through elevation of the diaphragm.

Circulation. Once adequate pulmonary ventilation is established attention should be turned toward the circulation. An intravenous infusion of 5 per cent glucose in water should be started and continued during the course of treatment; 2,500 cc. of glucose in water and 500 cc. of 5 per cent glucose in physiologic salt solution should be administered every twenty-four hours. If shock is apparent, plasma expander or whole blood may be indicated. The blood pressure should be maintained within the physiologic limits for the patient by the use of vasopressor drugs. A continuous infusion of 10 mg. of neo-synephrine® in 1 L. of 5 per cent glucose is advisable if a single intramuscular injection of 2 to 3 mg. of the same drug has not satisfactorily maintained the blood pressure. If a more potent vasopressor is required, L-nor-epinephrine (4 mg./L. of 5% glucose solution) is indicated. Neo-synephrine should be tried first because of the evanescent effect and the danger of local tissue necrosis following administration of L-nor-epinephrine. Both require careful titration and observation.

Gastric Lavage. Considerable quantities of unabsorbed narcotic may remain in the stomach for many hours. These can be removed by passage of a large-bore Levin tube with careful aspiration of the gastric contents, using 10 to 20 cc. amounts of physiologic salt solution for aspirating fluid. Regurgitation of stomach contents or aspirating fluids must be anticipated. In deep coma it is best to prevent aspiration of gastric contents by passage of a cuffed endotracheal tube during the period of gastric lavage. The gastric fluid removed may be analyzed for barbiturate or other suspected narcotic.

Catheterization of the Urinary Bladder. Urinary bladder distention should be guarded against by the insertion of an indwelling catheter or intermittent catheterization. This also permits better appraisal of urinary output.

Prevention of Infection. Antibiotics should be injected prophylactically soon after therapy is instituted. This will minimize pulmonary and other infections.

Damage to the Eyes and Lips. Care should be exercised to prevent this. The eyes may be taped shut. The lips should be lubricated to prevent

drying and cracking. Attention must be paid to oral hygiene.

Comment. Most of the proponents of analeptic therapy stress that good supportive treatment is required in addition to analeptics. The patients whose records are summarized in Table II have apparently had at least reasonably adequate supportive therapy; the analeptic regimens have varied, however, according to clinics from which the data have been collected.

DANGERS OF TREATMENT WITH ANALEPTIC AGENTS

Data are available to indicate that there are dangers associated with the use of stimulant drugs. The following complications may be anticipated: convulsions, vomiting with aspiration of gastric contents, and cardiac arrhythmias.

Convulsions with subsequent secondary central depression are the most feared complications. Roche et al.[15] reported that 20.3 per cent of their patients treated with picrotoxin had convulsions; Riishede[11] indicated that two of forty-three patients treated with nikethamide had convulsions, and in sixteen of forty-three patients with severe poisonings tremor, quivering, muscular rigidity and trismus developed often necessitating withdrawal or reduction in amount of the analeptic employed. The latent period between the injection of picrotoxin and the occurrence of maximal stimulant effect often makes convulsions difficult to predict or prevent. Bleckwenn et al.[16] mentioned that convulsions occurred thirty minutes after injection of a single dose of picrotoxin. This suggests that continuous injection of picrotoxin on a milligram per minute basis until twitching occurs is unwise. Intermittent injection appears to be a less hazardous method.[14,17]

Occasionally, unexpectedly small doses of analeptics may precipitate convulsions when coma has been enhanced by anoxia superimposed on the narcosis produced by relatively small doses of barbiturates.[17,29] Stimulant drugs may cause irreparable brain damage during anoxia by increasing cerebral oxygen demand[18] in excess of available oxygen supply. They may also hasten destruction of cells already damaged by oxygen lack by further increasing their metabolism. Analeptics should not be administered in the presence of hypoxia and are contraindicated under circumstances in which prolonged anoxia has existed.

Another common complication is vomiting, with the danger of aspiration of gastric contents. Riishede[11] reported vomiting in 42 per cent of forty-three comatose patients treated with nikethamide and 7 per cent of severe cases in which amphetamine was employed. Comparable figures with metrazol and picrotoxin have not been obtained but vomiting is not uncommon following the use of these drugs.

Reed, Driggs and Foote[14] have focused attention upon the high incidence of cardiac arrhythmias occurring in patients treated with picrotoxin or amphetamine and caffeine. Fourteen of twenty-eight deaths in one group of 209 patients were associated with tachycardia; all patients had received two of the three drugs. In twelve patients in the non-fatal group who had all been given large doses of the same analeptics, arrhythmias developed; six patients had cardiac rates above 140 per minute. In another group of ninety-one patients treated with restricted doses of amphetamine and caffeine and unlimited doses of picrotoxin as indicated, arrhythmias developed in fourteen. One of these cases seemed clearly to be due to picrotoxin. In this connection it is of interest to note that Jones, Dooley and Murphy[13] reported that two of three deaths were in patients known to have cardiac disease and "both had acute congestive failure of the heart after receiving picrotoxin."

Abnormalities of cardiac rhythm are prone to occur in barbiturate poisoning even in the absence of analeptic drugs. Kirkegaard and Norregaard[7] observed that thirty-nine of fifty-four patients poisoned with barbiturates had abnormal cardiac rhythms. They believed these to be due to myocardial anoxia. If such abnormalities are commonplace in barbiturate poisoning, caution should be exercised in the use of large doses of stimulant drugs.

It is apparent that the decision to treat barbiturate poisoning with analeptic drugs carries with it the risk of additional danger to the patient.

FACTORS LIMITING RECOVERY FROM NARCOTIC POISONING

No matter what the method of therapy, some patients will succumb after ingesting large amounts of barbiturates. A consideration of factors adversely affecting recovery is therefore important in respect both to prognosis and therapy.

Factors of importance include the time interval elapsing before treatment is begun, the dose

ingested, the rapidity of absorption of this dose, tissue damage secondary to anoxia and concomitant ingestion of other depressants, for example, alcohol.

The longer the interval between ingestion of large doses of narcotics and the onset of treatment, the poorer the prognosis. One of the advantages of the Copenhagen Center is the indoctrination given to physicians and the police. Every patient in coma is immediately rushed to the Center. Closer cooperation between the public, general practitioners and hospitals in America might help to reduce mortality from all forms of poisoning.

A second factor limiting recovery may be the rapidity of absorption of the ingested drug.[17] A relatively small dose of barbiturate may be fatal if conditions favoring quick absorption of the drug from the gastrointestinal tract prevail. A rapidly rising blood concentration depresses respiratory and circulatory centers, producing anoxemia and hypotension; both factors reduce the supply of oxygen to the brain. During anoxia, the brain is more sensitive to narcotics,[29] and death may ensue although the ingested amount of barbiturate be small.

A third limiting factor often overlooked in discussions on the treatment of barbituate poisoning is the part played by the anoxia which follows attendant respiratory depression or obstruction.[17,19] Sometimes it is impossible to separate the effects of the narcotic and those of anoxia but occasionally areflexic patients thought to be in deep barbiturate coma improve following establishment of adequate pulmonary ventilation. Prolonged exposure of the brain to low concentrations of oxygen may produce irreparable damage. Inspection of the histories of Nilsson's three deaths[4] reveals that severe cyanosis was prominent in each patient. These patients could have suffered central anoxic damage which prevented recovery.

Anesthetists are aware that severe anoxia during anesthesia often prolongs the recovery period. Also, it is a common observation that if cardiac arrest follows an episode of severe hypoxia, the chances of the patient's recovery are decreased, even though immediate thoracotomy and cardiac massage be performed. This is not true of cardiac arrest occurring in adequately oxygenated patients. Unconscious patients, regardless of the cause of coma, develop respiratory obstruction easily and accumulate secretions in their respiratory tracts, thereby becoming hypoxic. Anoxia under these conditions is just as destructive as that during anesthesia. Deepening coma twenty-four to forty-eight hours after ingestion of barbiturate suggests central anoxic damage.

Ingestion of usually sublethal doses of barbiturate may be associated with death in the presence of alcoholism or the concomitant ingestion of alcohol.[21] The mechanism of this synergism is not fully explained.

DISCUSSION

For some reason, many physicians confronted with patients suffering from suspected barbiturate poisoning immediately think of analeptics. These drugs are therefore often instituted in the first part of the treatment rather than in the last. Instances of this have been reported before.[17]

The following case is another example: A white man, age fifty-seven years, had known Parkinson's disease for ten years. He also had effort angina and periodic depression because of his illness and a constant substernal burning sensation. Early one morning, because of despondency, he ingested 2.9 gm. of sodium amytal. Seven hours later he was found to be comatose and was rushed to the hospital. There he was observed to have deep, slow, stertorous respiration with sounds characteristic of secretions in the pharynx and trachea, and coarse rales in the chest. The nail beds were blue. His pupils reacted to light. There was very slight response to questioning. He was seen by a resident and an interne in the receiving ward. The interne suggested calling for help to clear the respiratory tract of secretions and to administer oxygen. The resident demurred and proceeded to prepare metrazol for injection. At the interne's insistence an anesthesiologist was called. When the latter arrived, the patient's nail beds were still blue in spite of nasal oxygen which had been started. Aspiration of copious quantities of thick, purulent material from the tracheobronchial tree was associated with vigorous coughing on the patient's part. The chest cleared remarkably and the color improved immediately thereafter. Further therapy consisted solely of oxygen by nasal catheter, intravenous fluids and penicillin. The patient recovered completely in twenty-four hours.

Many patients included in series in which analeptics have been utilized may have been those in whom stimulant drugs had been used in the presence of anoxia and hypotension. While

the data presented in Table I support the fact that the mortality in patients poisoned with barbiturates and treated only with supportive therapy is lower than the mortality in patients who have received analeptics, it ignores the possibility that the latter group may not have had equivalent supportive therapy. It is noteworthy that when good supportive therapy preceded analeptic therapy (for example, Riishede's amphetamine group[11] and Reed, Driggs and Foote's Part II group,[14]) the mortality was still slightly higher than those with supportive therapy alone. (Table I.)

TABLE III
EFFECT OF IMPROVED SUPPORTIVE THERAPY*

	Cases	Deaths	Mortality (%)
Part I:			
Non-standardized supportive therapy; unrestricted analeptics	209	28	13.4
Part II:			
Standardized supportive therapy; partially restricted analeptics	91	5	5.5

* Data from Reed, Driggs and Foote.[14]

The data of Reed, Driggs and Foote[14] indicate how much can be accomplished by improvement in supportive therapy. Part I of their report concerned a series of barbiturate-poisoned patients in which those with light narcosis received no analeptic and those with deeper narcosis received large doses of amphetamine and caffeine with or without picrotoxin. Part II concerned similar patients given a standardized regimen of supportive therapy with meticulous attention to adequate pulmonary ventilation and support of the circulation. Amphetamine and caffeine were administered more carefully, with a maximum of 300 mg. amphetamine or 6 gm. caffeine every twenty-four hours. Picrotoxin was given as indicated without restriction. The results summarized in Table III show a considerable diminution in mortality in the latter group.

It is agreed that comparison of treatment in one series of poisoned patients versus another series is difficult. The lack of standardization of basic treatment discussed is just one of the reasons. A second is the inadequacy of criteria for classification of the severity of poisoning. Each author has established his own criteria which often contradict those of others. A detailed classification on the basis of clinical appearance is helpful, but the following tests might be informative: (1) response to inhalation of 10 per cent carbon dioxide (failure to observe hyperpnea suggests a poorly functioning respiratory center); (2) response to inhalation of 100 per cent oxygen (seeking oxygen apnea); (3) response to the intravenous injection of a test dose of 10 per cent metrazol (for example, 4 to 5 cc.); (4) electroencephalographic tracing;[20] and, (5) blood barbiturate levels.[21]

Barbiturate poisoning with longer-acting barbiturates such as barbital and phenobarbital may be associated with a higher mortality than that with the shorter acting barbiturates more commonly seen today.[22] Thus it is even more difficult to compare old and new data.

A comparison of data on the basis of dose-weight relationships has been suggested.[22] Such factors may be important in the laboratory where animal experiments can be carefully controlled and conditions standardized, but results vary even from laboratory to laboratory.[23] Standardization in man is impossible. The majority of patients with overdoses of barbiturates are in the middle age group or older,[4,14] either mentally or physically ill, possibly addicted to alcohol or other drugs, and in various states of nutrition. The time factor between the ingestion of drug and onset of treatment may vary, as may intervening periods of anoxia. Finally, factors that facilitate a rapidly rising blood level of ingested drugs may exist. A dose-weight relationship is applicable only to a specific set of conditions. Under the variety of circumstances listed for man, comparison of results of treatment based on such a relationship is not likely to result in significant conclusions.

Supportive treatment in barbiturate poisoning is ideally handled in postanesthetic recovery rooms. The Copenhagen Narcotic Center consists essentially of a group of recovery rooms, each equipped and attended by a staff of physicians and nurses trained in the care of the unconscious patient. Treatment afforded is that provided by physicians accustomed to caring for patients in the postoperative period. Although victims of barbiturate poisoning are usually admitted to medical services, problems involved in their care are more familiar to anesthetists. It is urged that these specialists be asked to participate in the treatment of these patients.

The authors agree with the statement by Koppanyi and Fazekas[24] that Nilsson has not

excluded the possible usefulness of analeptic drugs in the severely poisoned patient who has received good supportive therapy. The available data suggest that analeptics are valueless and even harmful, but for the patient in deep coma unresponsive to supportive therapy the data are not conclusive. However, the evidence clearly indicates that analeptics have no part in the treatment of other than severely poisoned patients. Since the majority of patients encountered with barbiturate narcosis do not fall into the severely poisoned group, it follows that treatment with stimulant drugs should be the exception and not the rule.

The authors vigorously protest statements that have appeared in the literature concerning the unquestioned therapeutic value of analeptics, for example, " . . . a physician in charge of a patient with severe barbiturate poisoning who fails to avail himself of metrazol and picrotoxin and depends on merely non-specific general supportive therapy takes a great deal of responsibility on himself";[22] or, "Metrazol and picrotoxin are still the most practical and valuable therapeutic weapons for the treatment of acute barbiturate poisoning."[24] Such remarks are not supported by available data obtained in man, are misleading to the physician, and potentially dangerous to the majority of patients poisoned with barbiturates.

Mention must be made of two newer methods of treating barbiturate poisoning. The first is cerebral electrostimulation,[25] the second is hemodialysis.[26,28,29] The second technic seems particularly promising. Walsh et al.[26] found that barbiturates could be removed fifteen to twenty-five times more effectively by the artificial kidney than via normal renal excretion. Sufficient data from patients treated by either method have not appeared so that their effectiveness cannot be judged. Results of treatment of larger series of patients will therefore be awaited with interest.

CONCLUSION

On the basis of the available evidence, supportive therapy alone is the method of choice in treating barbiturate poisoning. Analeptics appear to be without value and may even increase the hazard of narcosis by causing convulsions, cardiac irregularities and vomiting. The general problem is similar to that of treating a post-anesthetic comatose patient and it is suggested that a physician anesthetist participate in the treatment of all cases of narcotic poisoning. The complicating factor of cerebral anoxia is discussed. If anoxia has been a prominent part of the patient's clinical course, analeptics are contraindicated.

REFERENCES

1. Report to the Council on Pharmacy and Chemistry. Status of picrotoxin. *J. A. M. A.*, 10: 354, 1936.
2. Report to the Council on Pharmacy and Chemistry. Present status of picrotoxin in poisoning by the barbiturates. *J. A. M. A.*, 112: 431, 1939.
3. Eckenhoff, J. E., Schmidt, C. F., Dripps, R. D. and Kety, S. S. A status report on analeptics. *J. A M. A.*, 139: 780, 1949.
4. Nilsson, E. On treatment of barbiturate poisoning. *Acta med. Scandinav.*, suppl. 139, 1951.
5. Editorial. Respiratory problems of barbiturate poisoning. *J. A. M. A.*, 147: 874, 1951.
6. Clemmesen, C. and Bie, J. Centralization of the treatment of cases of hypnotic intoxication. *Ugesk. f. læger*, 112: 501, 1950.
7. Kirkegaard, A. and Norregaard, S. Electrocardiogram in severe acute barbiturate poisoning. *Acta med. Scandinav.*, 140: 119, 1951.
8. Dam, W. and Zwergius, E. Laryngeale komplikationer efter langvarig endotracheal intubation at narkotisk forgiftede patienter. *Nord. med.*, 47: 1095, 1952.
9. Locket, S. and Angus, J. Poisoning by barbiturates: success of conservative treatment. *Lancet*, 1: 580, 1952.
10. Larsen, E. and Poort, R. Narkotiske forgiftninger. *Ugesk. f. Laeger*, 114: 589, 1952.
11. Riishede, J. Treatment of acute barbiturate poisoning. *Lancet*, 2: 789, 1950.
12. Watts, J. C. and Ruthberg, J. Nikethamide in barbiturate poisoning. *Ann. Int. Med.*, 29: 1104, 1948.
13. Jones, A. W., Dooley, J. and Murphy, J. R. Treatment of choice in barbiturate poisoning. *J. A. M. A.*, 143: 884, 1950.
14. Reed, C. E., Driggs, M. F. and Foote, C. C. Acute barbiturate intoxication: a study of three hundred cases. *Ann. Int. Med.*, 37: 290, 1952.
15. Roche, M., Wynne, L. C. and Haskins, D. M. Therapy of acute barbiturate poisoning: report of three cases. *Ann. Int. Med.*, 33: 73, 1950.
16. Bleckwenn, W. J., Hodgson, E. R. and Herwick, R. P. A clinical comparison of picrotoxin, metrazol and coriamyrtin used as analeptics and as convulsants. *J. Pharm. & Exper. Therap.*, 69: 81, 1940.
17. Conferences on Therapy. Treatment of barbiturate poisoning. *Am. J. Med.*, 1: 93, 1946.
18. Schmidt, C. F., Kety, S. S. and Pennes, H. H. The gaseous metabolism of the brain of the monkey. *Am. J. Physiol.*, 143: 33, 1935.
19. Conferences on Therapy. Treatment of the patient in coma. *Am. J. Med.*, 14: 469, 1953.
20. Brazier, M. A. B. and Finesinger, J. E. Action of barbiturates on the cerebral cortex: electroencephalographic studies. *Arch. Neurol. & Psychiat.*, 53: 51, 1945.

21. Fisher, R. S., Walker, J. T. and Plummer, C. W. Quantitative estimation of barbiturates in blood by ultra-spectrophotometry. II. Experimental and clinical results. *Am. J. Clin. Path.*, 18: 462, 1948.
22. Koppanyi, T. and Fazekas, J. F. Acute barbiturate poisoning: analysis and evaluation of current therapy. *Am. J. M. Sc.*, 220: 559, 1950.
23. Barlow, O. W. The effectiveness of therapeutic measures after poisoning with sublethal and lethal dosages of barbital in the rabbit. *J. Lab. & Clin. Med.*, 23: 601, 1938.
24. Koppanyi, T. and Fazekas, J. F. Pharmacotherapeutic nihilism in the treatment of acute barbiturate poisoning. *Am. J. M. Sc.*, 224: 577, 1952.
25. Robie, T. R. Immediate treatment of barbiturate poisoning. *J. Med. Soc. New Jersey*, 47: 370, 1950.
26. Walsh, W. F., Kyle, L. H., Doolan, P. D. and Jeghers, H. J. Treatment of barbiturate poisoning by hemodialysis. *Am. J. Med.*, 13: 104, 1952.
27. Alwall, N., Lindgren, P. and Lunderquist, A. On the artificial kidney. II. Treatment of severe phenobarbital poisoning in rabbits. *Acta med. Scandinav.*, 143: 299, 1952.
28. Leonards, J. R. and Sunshine, I. Removal of barbiturates from the blood by the artificial kidney. *Federation Proc.*, 12: 237, 1953.
29. Meyer, L. Increased sensitivity for opiates and barbiturates in anoxia. *Acta med. Scandinav.*, 142: 256, 1952.

Seminar on Allergy

Life Stress and Allergy*

STEWART WOLF, M.D.
Oklahoma City, Oklahoma

BRIEFLY stated, it appears that tissue reactions occurring in response to threatening life experiences may be nearly identical with those resulting from the action of antigen on specifically sensitized tissue. Although the fundamental mechanisms of the two appear to differ widely, they may complement each other and together or separately induce the same symptomatic pattern.

A consideration of emotional factors in allergy requires a basis of mutual agreement as to the definition of allergy. Much confusion in the past has derived from discussions in altogether different frameworks using the same terminology. Von Pirquet who first introduced the term allergy shortly before the turn of the century assumed an interaction between antigen and antibody demonstrable by *in vitro* serologic tests as the basis for allergy.[1] Today this same conception is offered to explain immunity. Thus a positive reaction to the Widal test would indicate immunity to typhoid fever but would certainly not provide evidence of allergy. Nevertheless Harris and Harris, in the opening paper of this series, stuck to the original von Pirquet conception and considered the problems of origin and mechanism of action of antibodies as the fundamental basis for allergy.[2]

From another viewpoint, the tissue pathologist thinks of allergy in terms of the lesion centering about small blood vessels and characterized by vasodilatation, transudation of proteinacious material, tissue edema, infiltration with wandering cells, especially eosinophils, and often by hyaline degeneration of some of the tissue components. The picture in many ways resembles that of inflammation. The pathologist designates such a lesion as allergic if it can be produced by the introduction of a substance to which the organism has been previously exposed and is presumably "sensitized." The term allergic is thus applicable even in the absence of serologically recognizable circulating antibodies. Rather it is assumed that there are "fixed" antibodies in the tissue although repeated extraction of "sensitized" tissues has failed to reveal such substances. The work of Godlowski suggests that the nature of allergy is not precisely similar to the antigen-antibody combinations which take place in lymphoid tissues and in serum and which are recognized as immune responses.[3] He considers that in allergy the antigen disrupts the chemistry of the sensitized cell. The antigen is thought to reach the sensitized tissue because of its failure to be neutralized by circulating immune antibodies.

The tubercle, the Aschoff body, the lesions of glomerular nephritis and those of collagen diseases are often called "allergic." Such lesions are no longer thought to be specific for certain causative agents. This implication first evolved quite naturally from the studies of Virchow but today it is generally recognized that the same tissue reaction may follow a variety of noxious stimuli. The experimental findings of Selye and his concepts would allow for the occurrence of such vascular lesions and tissue damage in response to situational stresses which owe their force to their significance to each person and are hence mediated through the interpretive areas of the brain.[4] Even the tubercle is known to be produced by activating forces other than the tubercle bacillus and the Aschoff body by agents other than rheumatic fever.[5,6]

The third, or clinical conception of allergy, although overlapping, lies in an altogether different framework from the two already mentioned. It deals mainly with symptoms and diseases resulting from tissue reactions which are largely reversible. The designation of these reactions as allergic rests on the assumption that they result from contact with an agent to which earlier sensitization has taken place. Histamine-

* From the Department of Medicine of the University of Oklahoma and the Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma.

induced vascular changes serve as a prototype for clinical allergy although there is not acceptable evidence that histamine is implicated in the process. Neither have antigen-antibody reactions been demonstrated in most cases. Attempts have been made to demonstrate a specific tissue sensitivity by the use of the skin test but since specific tissue sensitivity may exist in one locality in the body but not in another, the correlation of positive reactions to skin tests and the historical implication of an offending agent in hay fever or asthma is not high.

Various bodily disorders such as rhinitis, asthma and urticaria are attributed to allergy because they may be induced by bringing the patient in contact with certain inhalants such as dust, pollens and danders as well as with certain powders and oils and other normally non-irritating substances. Some gastrointestinal symptoms are also attributed to allergy when they can be induced by eating fish, strawberries, milk, eggs and the like. Such disturbances, often related to sensitization of tissue and perhaps by way of antigen-antibody combinations may just as readily result from cholinergic neural impulses, still essentially reversible but capable of producing symptoms, inviting complications and even leading to death.[7]

In view of the fact that tissue sensitivity can be demonstrated in denervated areas and even in excised tissues, it is unlikely that allergy is a neural phenomenon.[8] On the other hand the possibility remains that the tissue response to an antigen may be modified by neural and other forces acting on the tissue at the same time.

If the term allergy is confined to antigen-antibody reactions, there may be an emotional component, but it has not been demonstrated. If allergy describes the vascular engorgement, capillary dilatation and escape of fluid into the tissue spaces which characterize these conditions and which produce the narrowing of bronchioles in asthma, the nasal obstruction of vasomotor rhinitis and the cutaneous lesion of urticaria, the evidence implicating meaningful situations is as convincing as that which implicates pollens or foods.[9–14] Most of the published data relating life situations to allergic reactions are concerned with this clinical conception of allergy.

The distinction between the pathologic and clinical concepts of allergy makes it difficult to determine whether life stress may simulate or induce allergic manifestations. Perhaps agreement can be reached as to the nature of allergy if the term is reserved to describe a bodily disturbance which occurs because of contact of a substance with which earlier contact has produced a specific tissue vulnerability. In this strict definition of allergy, meaningful life experiences could have, of course, only a figurative role unless they were connected in some way with increasing reactivity of tissues. As pointed out earlier it is not necessary to relate the phenomena of allergy to life stress but rather to postulate that the same type of tissue response may occur as a stress reaction or on the basis of allergy and that the two may be complementary or that they may act together to reinforce other noxious stimuli.

EXPERIMENTAL EVIDENCE

The nasal mucosa of man was studied by Holmes and associates after exposure to a variety of noxious stimuli, tangible and symbolic.[9] While the nasal membranes were under observation, subjects were made to inhale the fumes of ammonium carbonate, to sit in a cold atmosphere in light clothing, to inhale pollens, to undergo constriction of the head by a tight steel band and to engage in a lively discussion of important personal conflicts. All of these maneuvers were found to be capable of inducing nasal hyperemia, swelling, hypersecretion and obstruction with sneezing, associated lacrimation and suffusion of conjunctival vessels. Increased numbers of polymorphonuclear leukocytes and eosinophils appeared in the nasal secretions and histopathologic examination of the turbinates revealed a characteristic tissue edema with vasodilatation and hyperfunction of mucous glands.

It was particularly striking in the studies of Holmes and associates that those subjects who displayed a high degree of pollen sensitivity were, for the most part, highly reactive to other noxae, including life situations. In clinical attacks it was usually possible to identify more than one factor at work. It was also striking that the line between allergic and non-allergic patients was found to be a broad one of degree. Holmes and Treuting and their collaborators observed their subjects in a specially constructed pollen room in which ragweed pollens could be circulated without the knowledge of the subject.[11] It was found that while patients with seasonal ragweed hay fever could be made to display nasal engorgement with very little pollen in the air, the nasal membranes of nearly all

ordinarily insensitive persons could be made to swell if very large quantities of pollen were circulated. Thus although it is clear that the tissues of some people are far more susceptible to allergens than are the tissues of others, it would appear that some degree of tissue sensitivity exists in all people who have had earlier experience with pollens and that an allergic reaction can be produced in almost anyone with an overwhelming dose of antigen. This quantitative factor has been frequently observed in the case of food allergies. In persons who ordinarily eat sea food or strawberries with impunity, urticaria may develop when unusually large amounts of the materials are ingested.

The tissue reactions which were initiated or aggravated by mechanisms other than those involving specific tissue sensitivity appeared to depend upon direct local irritation as in the case of ammonium carbonate, or on neural impulses reaching the nasal membranes over their parasympathetic innervation as in the case of stressful interviews. These studies led to the concept of nasal reactors and non-reactors falling at either end of a normal distribution curve. The reactors resembled one another not only in terms of their labile nasal mucosae with readily mobilized engorgement and obstruction in response to irritating fumes, atmospheric cold, pollens and frustrating situations but also they resembled one another temperamentally. The subjects who were nasal reactors were found to be essentially defensive, insecure, sensitive, dependent people who talked with difficulty about relevant personal matters and who seldom took positive steps to improve their state. A lively show of love and affection was a basic requirement and was readily accepted but they seemed unable in turn to give sympathy, warmth and support to others. In many who were deprived of devotion and tenderness in early life, events which threatened such emotional support in later life often induced an exacerbation of the defensive reaction with nasal engorgement. Such persons were quick to react to threatening situations with feelings of intense humiliation and many of their attitudes and behavior patterns were designed to protect their sensitive feelings by "keeping the peace, avoiding the issues and doing for others." When their precarious security props were jeopardized, the content of the ensuing state of conflict included, in addition to humiliation, intense resentment, frustration and guilt. They were often unable to admit or to express feelings of hostility or anger but rather resorted to weeping and aggressive and desperate clinging to that which lent them security. In general, these persons who displayed a prominent pattern of nasal engorgement and obstruction appeared to be shutting themselves off from their environment in a figurative as well as a literal sense. Respiration consists of an in and out circulation of air through the respiratory passages. "Shutting out" thus involves equally a "shutting in." In effect the organism diminishes its exchanges with the environment. A person limits the extent of his participation in the situation about him. Thus insulated he takes in less and gives out less. "Shutting out" then becomes a part of an over-all reaction of non-participation and its "shutting in" aspect may include the repression of resentments and conflicts.

As in dealing with noxious gasses and dust, the infant may find the behavior pattern built a ound weeping an effective method of gaining succor from a hostile environment. As the infants grows he may perpetuate the weeping pattern with his conjoint behavior patterns and feeling states as a way of life, despite the fact that it becomes progressively less effective and more inappropriate as a protection against symbolic threats and assaults. The complete weeping pattern involving both eyes and the nose often persists in women into adult life but in men the impact of cultural conditioning may limit the manifestations of this to the nose. This concept may resolve the controversial views with reference to the relation of personality development to the allergic state. While personality and life experience may have nothing to do with the establishment of specific tissue sensitivities, they may correlate well with the relative reactivity of a given tissue or organ. Thus nasal reactors appeared to be set apart from their fellows by virtue of their general attitudes and points of view about life. There was no distinct personality profile but rather a recognizable uniformity of attitude in dealing with experiences and challenges of day-to-day living.

Observations on asthmatic subjects by Treuting and Ripley[10] and by others supported the findings of hay fever sufferers. It was noted that the nasal and bronchial mucosae are parts of a continuous membrane which in places is almost histologically identical. Attacks of asthma were induced in the pollen room and during interviews covering stressful topics. The additive effects of these two stimuli were clearly demon-

strable. The pertinence of sensitization of bronchial tissues to allergens was not well reflected by skin tests.

Asthma, perhaps more than any of the other "allergic" diseases, has interested psychiatrists and impressed allergists with its psychologic aspects. Although the pertinence of inhalants has been established by experimental production of asthmatic attacks, the prominence of personality factors has been recognized by a large number of observers.[15–20] In 1941 French and Alexander proposed a psychodynamic formulation in which asthma was considered to be akin to a stifled cry.[21] Not only have asthmatic attacks been induced by stress interviews but also by hypnotic suggestion.[22]

The similarity of the tissue disturbance in rhinitis and asthma is paralleled by common features in personality adaptation and by the fact that the two conditions are often linked.

Marcinowski[23] found antecedent nasal obstruction and rhinorrhea in a large series of patients with asthma and believed that the latter was merely an extension of the former process. "Asthma begins in the nose and ends in the bronchi" has been a frequently expressed dictum supported by general clinical experience.[24–25] The pathologic changes which occur in both upper and lower respiratory channels are similar in character. First there occurs vascular engorgement and edema associated with increased production of mucus and often infiltration with eosinophilic or polymorphonuclear leukocytes. When the process becomes intense and sustained, a substitution of mucus-producing goblet cells for the ciliated columnar cells occurs in the epithelium of both the nose and the bronchi. This process results in loss of the protective ciliary action. Finally, the difficulty in removal of the viscid secretion in asthma may result in death from asphyxiation.[26]

RHINITIS AND ASTHMA

Experimental observations on a patient with both rhinitis and asthma illustrated with some clarity the association of the two conditions and their connection with life adjustment.

Case Report

CASE I. M. B., a thirty-six year old housewife, complained of attacks of dyspnea associated with dry cough and wheezing for the past six months. Her parents were Russian Jews who came to this country before World War I. Her father had been a rabbi. He was educated and gentle but an extremely forceful character. Her mother was less educated and blindly enforced the policies of the father. The parents were both well and lived in a Jewish section of Brooklyn where they enjoyed a secure social and economic status. The patient was the sixth of seven children. The first three children were girls, fourteen, eleven and eight years older than the patient, respectively. All were married to successful Jewish business men, were apparently happy and enjoyed the good favor of the family. Of her three brothers, two were older than the patient and one was three years younger. The oldest brother was an accountant, the second a factory foreman and the youngest a lawyer. The boys also enjoyed ostensibly happy homes and the favor of their parents.

The patient's early development was not unusual. She was a cheerful, friendly, outgoing, bright girl who was the favorite of her parents and apparently also of the older siblings, being a girl among several boys and the gayest and brightest of the children. Because of her precocity she was advanced rapidly in school. She was fun-loving and resisted this rapid scholastic advancement but since she appeared to be the brightest of the children, the father quietly insisted that childish pleasures were ephemeral and should be subordinated to more important intellectual achievements. Accordingly, in high school she was the youngest of her contemporaries. She was called the "baby" by her family and friends. She was denied the gay times which many of her girl friends enjoyed, presumably because of her younger age. "Those things aren't important," said her father. "Wait until you can enjoy them."

At sixteen she graduated from high school and was eager to enter normal school with her classmates but was denied admission on the ground that she was too young. For the same reason she was not allowed by her family to become seriously interested in young men. Partly in protest against the thwarting of her plans to become a teacher she went to work as a bookkeeper. "I decided that was all I could do as long as they wouldn't let me continue on with my friends." She held this job until her marriage five years later. At seventeen she met and fell in love with a young Jewish lawyer whom she describes as being very similar to her father. "He had the same ideas. He was a philosopher. He said he wouldn't make love to me because I was too young for him. I was always too young." She told of her interest in this man only when she was under the influence of sodium amytal. His behavior was extremely frustrating since he would be very attentive at times, saying that he loved her and wanted her, but he failed to make sexual advances on the grounds that she was too pure and too young for him. Her other suitors were serious-minded Jews interested at the time in careers rather than in marriage.

At a social gathering she met a Roman Catholic

youth of French and Italian origin who appealed to her because he was gayer and more generous and carefree than other boys of her acquaintance. Her parents disapproved of this association on religious grounds. This man was nine years older than she, very attentive and had traveled around the world as a merchant sailor. Like Desdemona the patient was fascinated by the narratives of his travels. At twenty-two she finally married him secretly in defiance of her family's wishes. Lacking courage to tell them of the marriage, she continued to live at home. It was not until a month later that she announced her status and at the same time gave up active adherence to the Jewish faith. The patient's father accepted the marriage magnanimously yet with a martyred air, but her mother continued bitterly to disapprove it and refused to meet the husband. The patient thereupon left home. She looked earnestly to her husband for achievements which would vindicate her desertion of the family's pattern. Her hopes were not realized, however, since shortly after their marriage, for reasons of security, her husband obtained a job as a municipal garbage truck driver.

Following her marriage, the patient began to eat excessively and gradually became obese. Her mother-in-law, who had also opposed the union on religious grounds, continually interfered in her menage, holding that she was too young to manage her affairs. The patient felt that by becoming obese and "matronly" in appearance she might be considered more competent. Her weight increased from 115 to 169 pounds during the fourteen years of her marriage. Three years after their marriage the first child, a daughter, was born and six years later, a son. The patient hoped to be able to provide educational opportunities for the children so that they could raise their social standing in accordance with the usual Jewish pattern. Her husband did not share these ambitions or aspirations, however, and was unwilling to seek a more lucrative job so that they might be realized.

The patient worked hard at educating and training her children. In 1944, at the age of eight, her daughter was found to have diabetes. The patient reacted to this situation with considerable anxiety and disappointment. At that time she began having frequent nasal obstruction with difficulty in breathing through the nose, but without much increase in secretion. She felt that in view of this serious illness her daughter's future was in grave doubt. She considered it as a failure on her part and felt that she had betrayed her family tradition by electing the course of life which she had followed. Her nasal obstruction began suddenly when several other women in her presence were condemning a girl for overstepping conventions.

The cost of managing the diabetes aggravated her feelings of economic insecurity and the need to prepare separately all her daughter's meals made her feel that it was impossible for her to do remunerative work to help provide educational opportunities. Her conflict was enhanced when her daughter displayed an interest in graphic arts and an appetite for schooling. The following year the patient's nasal obstruction with its attendant difficulty in breathing was so troublesome that she underwent an operation for removal of nasal polyps. Following the operation she fared moderately well until November, 1945, when her son became ill with abdominal complaints characterized by attacks of pain which were puzzling to his physicians. His symptoms were identical to those which had led her daughter to the doctor so she feared that her son, too, might have diabetes. He was admitted to the hospital for consideration of operation. At this time the patient began to have attacks of wheezing during the night, at first while asleep and later at other times. Persistent respiratory distress ensued with accompanying dry cough.

Other troublesome situational factors at this time included a limited and fixed income. Her husband's meager salary had remained unchanged throughout the war while others of their acquaintance enjoyed the inflated earnings of war workers. She felt that she had little with which to compensate herself for having fallen from grace with her family. The children of her brothers and sisters seemed healthier and seemed to have a brighter outlook for "success" in life.

The patient was aware of none of these conflicts when she first came to the hospital for treatment. Most of them were brought out during interviews under sodium amytal. Most of them were denied when she was not under the influence of the agent.

Observation 1. On the occasion of this experiment the patient came to the hospital in a mild status asthmaticus which had been present for two days. She was having respiratory difficulty at rest and sibilant sounds and expiratory wheezes were heard over both sides of her chest. One-half gram of sodium amytal was administered intravenously. At the end of the five minutes required to inject the drug the patient was lying comfortably without respiratory distress or wheezing. No abnormal sounds were heard when her chest was auscultated. She was relaxed and jocular. When asked what was on her mind she said, "You're a very handsome doctor and you've been nice to me." When asked what her relationship with her mother had been, she said "Strict. She wasn't half as smart as my father. I used to sit and marvel at my father. You might as well call it worship. He had a sense of humor and he was a philosopher, very religious." At this point she lapsed into silence and had a serious, reflective expression on her face. The wheezing began again. She was asked to speak further about her father. "He's very kind and understanding, but he wouldn't let us do anything. He kept pushing me ahead in school and wouldn't let me have no pleasures. Nothing. He always said 'they don't mean nothing,' 'Wait until you can enjoy them better.' It was always 'wait,' 'put it off,' don't enjoy nothin' now'. . . . I got very, very old in the 14 years I've

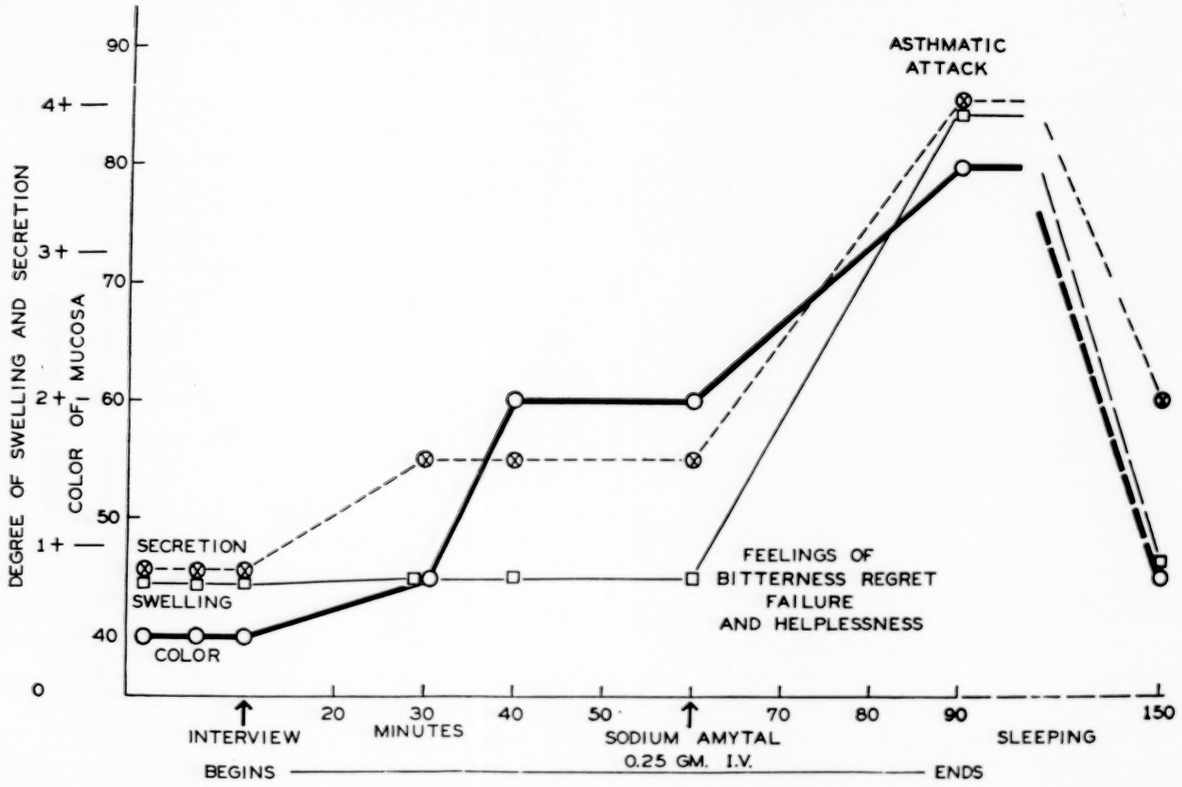


FIG. 1. Experimentally induced hyperemia, swelling, hypersecretion and obstruction in the nose associated with narrowing of the bronchial tubes during a discussion of topics provocative of feelings of emotional conflict.

been married. My husband is nice, but not learned. But he is interesting because he has been around so much." By this time five minutes of the interview had elapsed. Her wheezing was so severe that she had to sit up and had difficulty in talking. She spoke only when prodded. "I hoped things would go good with my children; that they wouldn't be wild like they are, and would grow up to be nice people."

At this point an attempt was made to divert the patient by jocularity and questions regarding what she would enjoy doing. "I'd like to go dancing," she said, in an embarrassed, half-smiling way, "I used to love to dance. Now I don't do anything. I never did much." Dancing and gaiety were then dwelt upon in a light and whimsical fashion. The patient relaxed again, lay prone while smiling, and her wheezing disappeared for the second time. After five minutes of relaxation and freedom from asthma, the subject of her old suitor was reintroduced. She began to wheeze again almost at once and became tense and serious. She seemed reflective and did not speak. When asked what she was thinking about she said, "He called me up to take me to one of his proms one day, when he told me the day before that I was too young to take out. So, I refused to go out, to prove to him that I was too young." Within one minute the wheezing was almost as marked as it had been before.

The patient was asked to get down from the table and once again it was possible to divert her by reference to her unsteady gait and by bantering about being drunk. It was suggested that she go to the cafeteria for a cup of coffee. At this time, about forty-five minutes after the beginning of the experiment, she was again relaxed, jovial and free from wheezing. An hour later she had largely recovered from the effects of sodium amytal but was still free from respiratory symptoms and was sent home; having been relieved of her asthma during relaxation and jocularity.

Comment: In this interview, after an asthmatic attack had been relieved during the general relaxation consequent upon the administration of sodium amytal, intravenously, the subject told for the first time of emotionally-charged events. This recital gave rise to feelings of remorse, guilt and resentment. Accompanying these circumstances she suffered a recurrence of her asthmatic attack. This was subsequently relieved and caused to recur again during preoccupation with conflicts.

Observation 2. Two days after the first experiment the patient was again seen with persistent wheezing and dyspnea but a slightly lesser degree. As on the previous occasion she was given sodium amytal intravenously. This time, while under the influence of the agent, she was told to pretend that she was eighteen years old and was asked to re-enact what might be going on in her life. "I am out dancing," she said,

"but I wouldn't see him again. I let him go because he stood my sister up." She indicated that she had more success in attracting young men than her sister but thought that she should take a secondary position. She told of having had pneumonia at the age of eighteen and, while ill, of having a dream in which an argument occurred between her right and left sides in which her left wanted to be serious and obedient and her right said "Don't be that way." She felt that her respiratory difficulty was centered in the right side of the chest. Auscultatory examination at this time revealed many more rhonchi and wheezes in the right side of the chest than the left. She also told of having been engaged to her lawyer suitor a year prior to her marriage, and that they quarreled because of her loyalty to a girl friend who was considered "fast." The erstwhile fiance had become engaged to another girl when the patient was married. "I might have been happier with him but I did not want to take orders from anyone." She added that she believed in fate, wanted to accept what came to her and tried to keep such thoughts out of her mind. Shortly after this she fell asleep. She tossed and turned a good deal in her sleep and continued to wheeze and was still wheezing when she awoke an hour and a half later. She said she had been dreaming about being young but could not be induced to give the details of her dream.

Observation 3. A week later the subject came to the hospital practically free of wheezing and feeling well. On this occasion her nasal membranes were examined and found to be moderately pale. (Fig. 1.) The turbinates were flat, and the airways free. She was asked to describe the events surrounding the discovery of diabetes in her daughter. "First it started with a pain in the right side low down," she said. "I took her to the doctor and he gave her medicine for her stomach gland. She was losing weight too. She looked awful. Finally, I took her to other doctors and they didn't know what it was. Then one day she went into a coma. I rushed her to the hospital, and when the doctor told me it was diabetes, I nearly passed out. I couldn't imagine what that was from, and I knew it didn't look too good for the future." By this time her wheezing had become slightly more prominent. Her nasal mucosae were now redder, but there was no evident swelling of the turbinates and the airways were clear. During the next twenty minutes the subject of diabetes was further pursued and her son's illness discussed. She was also asked why she had married her husband, since it required breaking with her family, her traditions and her religion. "I don't know why," she said. Her attention was called to the more favorable economic situation of her brothers and sisters and to the superior education available to their children. "I don't know much about them," she said. She seemed unperturbed and no further changes in her nose or chest were observed.

Accordingly, she was given 0.25 grams of sodium amytal intravenously. At first during the injection she was relaxed, smiled and her wheezing disappeared. Then the subject of her former fiance was introduced. "He was the only man I ever really loved," she said. She was then questioned concerning her reasons for throwing away her opportunities for marital happiness, economic security, productive offspring and favor with her family. She was reminded that she had lost her good figure and had become "fat," felt middle-aged, and had relatively little to look back on or forward to with satisfaction. She appeared grimly attentive and said very little, murmuring at intervals about having "stuck to it," having fought "prejudice and gossip," and several times she commented on her husband's kindness and sterling qualities. Her voice was weak. Wheezing was moderately severe and she coughed a great deal. By this time her nasal membranes had become bright red, swollen and turgid with profuse secretion, so that partial obstruction to breathing had developed on either side. Contact of the speculum with the now swollen membranes was painful. There was no further discussion and the subject fell asleep for an hour. On awakening there was still slight wheezing and an occasional cough. Her nose was filled with mucoid secretion. After she had cleared it by blowing, the membranes were again examined. The swelling had subsided almost completely and secretion was less profuse. The color was light pink again, and the airways were practically clear. Instrumentation with the speculum was no longer painful. The patient offered spontaneously that she now recognized that her symptoms were related to repressed emotional conflicts but that she did not see how her situational difficulties could be solved.

Comment: It is clear from these experiments and other data published elsewhere[27] that sodium amytal does not act directly on the mechanisms for bronchial or nasal obstruction. The drug appears to enable the experimenter readily to manipulate the experimental situation by focussing the patient's thoughts and preoccupations on one subject or another. Under the influence of sodium amytal, as under hypnosis, the subject becomes more than ordinarily capable of reacting to topics of threatening significance. The pattern of reaction in this subject to her troublesome life situation was clearly one of shutting out. She was unaware of most of her conflicts in her fully conscious state. Under sodium amytal she declared, "I try to keep such thoughts out of my mind." Certainly her nose and bronchial tree were doing their utmost to contribute to the shutting out process.

URTICARIA AND ECZEMA

Urticaria was studied experimentally by Graham who was not only able to correlate clinical attacks with difficult life experiences but also to induce urticarial lesions in his subjects during discussions of pertinent personal prob-

lems.[12] In line with an earlier demonstration by Scott[28] and by others[29,30] that positivity of skin tests may vary from time to time, Graham found that dermatographic skin as well as the ability of produce a wheal in the skin by histamine iontophoresis varied with the emotional state of the patient. Graham and his associates also reported similar studies relating to eczema in which measurable changes in the skin were correlated with meaningful life experiences.[13]

RELATION OF CONDITIONING TO "SENSITIVITY"

Evidence for specific tissue sensitivity is often based on the occurrence of symptoms following exposure to or ingestion of a supposed allergen. It has been shown experimentally that such a sequence of events may result from conditioning effects rather than the specific nature of the substance in question. The following three cases are examples of this.

Case Reports

CASE II. This fifty year old woman was being followed up in an allergy clinic as a classic example of milk sensitivity. Her chief complaints were "pressure" in her head, "poor thinking and memory," "vision not clear," "dizziness," abdominal cramps, nausea, hives and abdominal "bloating." The symptoms occurred within ten to twenty minutes after ingesting milk or milk products. It was stated that four drops of milk in a glass of water produced attacks of the nature described. She had had these attacks for eleven years, beginning after a caesarean section. The patient had "never liked milk" but had taken a great deal of it during this pregnancy, during which she gained sixty pounds. Soon after she was given a reducing diet, milk elicited the symptoms. Skin tests were positive to milk, tomatoes, peaches, peas, pork and lobster, but symptoms were associated only with the ingestion of milk. The patient's last ingestions of milk had been four days and eight days prior to the skin test.

On the occasion of the experiment, balloons were introduced into the stomach and duodenum. After a preliminary control period had established the approximate rate and amplitude of contractions, 50 cc. of whole milk were introduced into the fundus by stomach tube without the patient being able to observe what was being administered. She was told that she was being given water as a preliminary testing procedure. There was no significant change in the duodenal motility pattern and the patient exhibited no symptoms. About two weeks later the experiment was repeated. This time the patient was given 50 cc. of tap water and she was told that milk was being introduced. Nausea and abdominal discomfort developed following this suggestion, associated with some change in the duodenal motility pattern.

CASE III. A forty-five year old woman was studied who for twenty-eight years had had attacks of asthma within a few minutes after eating food prepared with cottonseed products, such as doughnuts. She also exhibited wheezing and dyspnea in rooms containing cotton-filled furniture. In addition she complained of abdominal cramps and nausea after eating mushrooms. Her skin and conjunctiva were sensitive to cottonseed extract. On an occasion when she knew that she was being tested, this patient was given 1 cc. of 1,000 units of cottonseed extract by mouth. Nausea occurred in nine minutes and lasted for twelve minutes. Three days later the administration of 10,000 units of cottonseed extract by mouth was followed by itchy nose and a severe asthmatic attack which persisted for thirty-six hours. No attempt was made to conceal from her that cottonseed was being given.

At a later date 5,000 units of cottonseed extract were given by stomach tube, the patient being told that it was water being used to test stomach motility. No symptoms ensued. Fifty minutes later, 50 cc. of water was given and the patient was informed that she was receiving mushrooms. Nausea, abdominal pain and bowel urgency occurred thirty minutes after the latter administration. These symptoms lasted for twenty minutes and did not recur.

CASE IV. This thirty-nine year old woman for about three months complained of wheezing, running eyes and nose, and hives soon after the ingestion of milk. Results of skin tests were positive to milk and fish. A stomach balloon was inserted and, after a control period during which motility of the stomach was observed, 50 cc. of milk were introduced. The patient was told that the introduced liquid was water. She was then told that a specimen of gastric secretion was to be taken but actually nothing was withdrawn. Her nasal mucous membrane was examined before and after the administration of milk and it was found that there was less secretion and congestion after the milk than before. She had no wheezing.

These cases illustrate the complexity of evaluating the relevant forces behind symptoms and tissue disturbances even in the presence of positive reactions to skin tests. They do not invalidate the role of specific antigens but they do illustrate the importance of a comprehensive evaluation of the personal history of each patient as a part of the study of his sensitivities.

THERAPY

By far the majority of papers on emotional factors in allergy deal with therapy.[31–34] Although no carefully designed therapeutic experiments have been reported there is widespread emphasis on the fact that psychotherapy is a

powerful tool in the management of patients with hay fever, asthma and urticaria. Even when specific tissue sensitivity has been established as an etiologic factor, attention to the patient's general adjustment is considered to be as relevant as is a concern with the offending allergen.

SUMMARY

Since careful recent surveys of the literature are available elsewhere,[35–37] this presentation has attempted to serve more as a commentary than as a review. Special emphasis has been placed on the experimental basis for a relationship between life stress and allergy.

In the literature concerned with the relationship between personality adjustment and the occurrence of so-called allergic disorders, one can recognize three somewhat different working concepts. The first suggests that a person's proclivity for developing specific tissue sensitivities is related to his life adjustment. The second makes a distinction between allergy and stress reactions but proposes that stimuli arising out of problems and challenges in day to day life are capable of inducing the same type of bodily disturbances which foreign proteins and other allergens are capable of inducing. Thus situational factors may combine with and reinforce the effects of allergens enhancing the end result in terms of tissue alterations and symptoms. The third proposition revolves around the general assumption that a relative lability in the behavior of certain bodily organs and tissues is related to a person's attitudes and way of life as well as perhaps to his genetic endowment. Hence, in such highly reactive subjects any appropriate stimulus, be it irritant, allergen or emotional challenge, might produce a disturbance great enough to be recognizable and symptomatic.

REFERENCES

1. von Pirquet, C. Klinische Studien über Vakzination and vakzinale Allergie. Leipzig, 1907. Deuticke.
2. Harris, T. N. and Harris, S. The genesis of antibodies. *Am. J. Med.*, 22: 114, 1956.
3. Godlowski, A. A. Enzymatic Concept of Anaphylaxis and Allergy. Edinburgh and London, 1953. E. & S. Livingstone, Ltd.
4. Selye, H. The alarm reaction. In: The Cyclopedia of Medicine, Surgery and Specialties, vol. 15, p. 15. Philadelphia, 1940. F. A. Davis Company.
5. Rich, A. R. and Gregory, J. E. Further experimental cardiac lesions of rheumatic type produced by anaphylactic hypersensitivity. *Bull. Johns Hopkins Hosp.*, 75: 115, 1944.
6. Reifenstein, G. H. Rheumatic-like lesions found in unselected autopsies. *Proc. Am. Fed. Clin. Research*, 4: 2, 1948.
7. Harper, R. Allergy and other stress-conditioned illness: suggested association with obsolete autonomic defense reflexes. *Brit. M. J.*, 1: 392, 1953.
8. Ebbeck, U. Die lokale vasomotorische Reaktion (L. V. R.) der Haut und der inneren Organe. *Arch. f. d. ges. Physiol.*, 169: 1, 1917.
9. Holmes, T. H., Goodell, G., Wolf, S. and Wolff, H. G. The Nose. Springfield, 1950. Charles C Thomas.
10. Treuting, T. F. and Ripley, H. S. Life Situations, Emotions and Bronchial Asthma. *J. Nerv. & Ment. Disease*, 108: 380, 1948.
11. Holmes, T. H., Treuting, T. and Wolff, H. G. Life situations, emotions and nasal disease: evidence on summative effects exhibited in patients with "hayfever." In: Life Stress and Bodily Disease. Baltimore, 1950. William & Wilkins Co.
12. Graham, D. T. The pathogenesis of hives. *J. A. M. A.*, 143: 1396, 1950.
13. Graham, D. T. and Wolf, S. The relation of eczema to attitude and to vascular reactions of the human skin. *J. Lab. & Clin. Med.*, 43: 238, 1953.
14. Graham, D. T., Wolf, S. and Wolff, H. G. Changes in tissue sensitivity associated with varying life situations and emotions; their relevance to allergy. *J. Allergy*, 21: 278, 1950.
15. Rogerson, C. H., Hardcastle, D. H. and Duiguid, K. A psychological approach to the problem of asthma and the asthma-eczema-prurigo syndrome. *Guy's Hosp. Rep.*, 85: 289, 1935.
16. Despert, J. L. Emotional factors in some young children's colds. *M. Clin. North America*, 28: 603, 1944.
17. Abramson, H. A. Somatic and Psychiatric Treatment of Asthma. Baltimore, 1951. Williams & Wilkins Co.
18. Miller, H. and Baruch, D. Emotional traumata preceding the onset of allergic symptoms in a group of children. *Ann. Allergy*, 8: 100, 1950.
19. Schwoebel, G. Psychosomatic studies on bronchial asthma: the character structure of the asthmatic. *Am. J. Psychotherapy*, 6: 214, 1952.
20. Wittkower, E. Psyche and Allergy. *J. Allergy*, 23: 76, 1952.
21. French, T. M. and Alexander, F. Psychogenic Factors in Bronchial Asthma. (Part I). Psychosomatic Monograph IV. Washington, 1941. National Research Council.
22. Bernstien, A. E. The Influence of Hypnosis upon the Allergic Reaction. Premier Congres International D'Allergie, 1: 839, 1951.
23. Marcinowski, J. Die Heilung eines schweren Falles von Asthma durch Psychoanalyse. *Jahrb. f. psychoanalyt. Forschungen*, 5: 529, 1913.
24. Derbes, V. J. and Engelhardt, H. T. The Treatment of Bronchial Asthma. Chapter by Fabricant, N. D.: Rinolaryngologic aspects of bronchial asthma. Philadelphia, 1946. J. B. Lippincott Co.
25. Egbert, J. H. Asthma, a nasal disease. *New York State J. Med.*, 89: 380, 1909.
26. Hilding, A. C. Relation of ciliary insufficiency to death from asthma and other respiratory diseases. *Ann. Otol., Rhin. & Laryng.*, 52: 5, 1943.

27. Wolf, S. and Ripley, H. S. Studies on the action of intravenously administered sodium amytal. *Am. J. M. Sc.*, 215: 56, 1948.
28. Scott, W. M. Anaphylaxis in the rabbit; the mechanism of the symptoms. *J. Path. & Bact.*, 15: 31, 1910–11.
29. Doerr, R. and Russ, V. K. Studien über Anaphylaxie. *Ztschr. f. Immunitâtsforsch. u. exper. Therap.*, 3: 706, 1909.
30. Weil, R. Studies in anaphylaxis. xiii. The activation of antibody by the cell. *J. M. Res.*, 32: 107, 1915.
31. Abramson, J. A. Report of the committee on psychosomatic allergy. *Ann. Allergy*, 2: 366, 1953.
32. Kaufman, W. A commonsense approach to psychotherapy in allergic practice. *Ann. Allergy*, 2: 291, 1953.
33. Miller, H. and Baruch, D. W. Psychotherapy in acute attacks of bronchial asthma. *Ann. Allergy*, 2: 438, 1953.
34. Groen, J. Treatment of bronchial asthma with the combination of ACTH and psychotherapy (group treatment). *Med. T. Geneesk.*, 98: 2212, 1954.
35. Ratner, B. Allergy, Anaphylaxis and Immunotherapy. Baltimore, 1943. Williams and Wilkins Co.
36. Gottlieb, P. M. Bronchial asthma: a review of the recent literature. *Ann. Allergy*, 2: 367, 1953.
37. Burden, S. S. The role of the psyche in allergic disease. *Ann. Int. Med.*, 43: 1283, 1955.

Clinico-pathologic Conference

Hypertension, Proteinuria and Edema

STENOGRAPHIC reports, edited by Amoz I. Chernoff, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior Medical students.

A TWENTY-FIVE year old Negro housewife (No. 259357) was admitted to the St. Louis Maternity Hospital on August 31, 1955. She had had enuresis until age sixteen and nocturia and polydypsia of two to three quarts per day thereafter. No other renal symptoms were noted until her first pregnancy two years prior to hospital admission. In the seventh month of gestation swelling of the eyes and ankles, and hypertension developed but there was no proteinuria. The patient was admitted to a hospital in another city where caesarian section was performed; she was delivered of a stillborn fetus. Three days postoperatively sudden impairment of vision developed and the patient had three generalized convulsions. Soon thereafter she felt better and was discharged from the hospital without medication after eleven days. Nocturia and polydypsia continued but the patient was able to work all day as a clerk without further ankle edema, although she was told by several physicians that her blood pressure was elevated. Her last menstrual period was thirteen weeks prior to admission to Barnes Hospital. Four weeks prior to admission she noted morning sickness, anorexia and a weight loss of thirty pounds. One week later, her blood pressure was found to be elevated to 240/140. Swelling of the eyes was again noted. She began to vomit soon after eating and was hospitalized at another institution for the nine days prior to admission here. At that institution her blood pressure was 240/140 and the eye grounds showed "retinopathy." Her urine contained 3+ protein; an Aschheim-Zondek test gave positive results; hemoglobin was 5.8 gm. per cent, non-protein nitrogen 68 mg. per cent and blood sugar, 123 mg. per cent. The patient was treated with ansolysen,® reserpine and three blood transfusions. Following this therapy the blood pressure fell slightly, the non-protein nitrogen rose to 112 mg. per cent and the hemoglobin rose to 8.0 gm. per cent. On August 31, 1955, she was transferred to St. Louis Maternity Hospital.

The patient did not give a history of scarlet fever, sore throat or hematuria. Family history revealed that her mother had died of hypertension.

Physical examination at the time of admission revealed the patient's temperature to be 36.5°C.; pulse, 80; respirations, 20; blood pressure, 200/120. The eye grounds showed blurred and edematous discs, multiple flame-shaped hemorrhages, many fluffy exudates, a "star-figure" of the macula, marked narrowing of the arterioles, and marked A-V nicking. The heart was not enlarged, the rhythm was regular, and there was a soft systolic murmur at the apex. The lungs were clear, and there was no edema. The cervix was congested and soft. The uterus was enlarged above the symphysis pubis and was soft. The deep tendon reflexes were normal.

Laboratory data were as follows: hemoglobin was 9.0 gm. per cent, and hematocrit 26 per cent; the following day repeat hemoglobin was 7.9 gm. per cent, and the red blood count 2.6 million per cu. mm. Urine specific gravity was 1.010, protein 2+, and the sediment contained occasional red cells, a few white blood cells in clumps, and occasional waxy casts per high power field. Urine culture revealed no growth. Roentgenograms of the chest were normal. Non-protein nitrogen was 120 mg. per cent, CO_2 28.9 mEq./L., chloride 84 mEq./L., creatinine 11.3 mg. per cent, total protein 5.7 gm. per cent, albumin 3.7 gm. per cent, globulin 2.0 gm. per cent. The frog test for pregnancy was negative on admission, but repeat tests on the third and fifth hospital days gave positive results. The serum contained 25 ASO units. A throat culture showed no beta hemolytic streptococci.

The patient was treated with reserpine and

apresoline,® and the blood pressure averaged 175/110. Her visual difficulty persisted and the fundi showed no change. The urine continued to show 3 or 4+ protein. On the sixth hospital day the uric acid was 11.9 mg. per cent, the non-protein nitrogen 140 mg. per cent. On the following day the patient complained of abdominal cramps and vaginal spotting, which persisted for two days when, after packing of the cervix, small fragments of tissue were passed which showed degenerating decidua and immature chorionic villi. On the eighth hospital day the CO_2 was 27.3 mEq./L. and the chloride was 77 mEq./L. Twenty-four hours later the non-protein nitrogen had risen to 155 mg. per cent, and the patient was vomiting irregularly. Uterine bleeding persisted. She was given parenteral fluids because of vomiting. The serum sodium was 124.4 mEq./L.; potassium, 4.3 mEq./L. On the eleventh hospital day the patient was transferred to the medical service.

Physical examination revealed the blood pressure to be 180/100, temperature 37.0°c., pulse 100 and respirations 16. She weighed 133 pounds. The fundi showed flat discs, narrowed and tortuous arterioles, and exudates about the macula with scattered hemorrhages in the right eye. The lungs were clear. Cardiac dulness extended 11 cm. to the left of the mid-sternal line in the fifth intercostal space. The rhythm was regular. The aortic second sound was markedly accentuated. There was a grade 2 high-pitched apical systolic murmur which radiated to the left axilla. There was no edema. The reflexes were hypoactive. The laboratory data revealed the following: hemoglobin, 6.0 gm. per cent; white blood cells, 9,100 per cu. mm.; differential count: eosinophil, 1; segmented forms, 80; lymphocytes, 16; monocytes, 3. A catheterized urine specimen showed 2+ protein and many white blood cells in the sediment; the test for sugar gave negative results. Occasional rods and cocci were found in the sediment, but a culture of the urine showed no growth. A stool was liquid, brown and guaiac-negative. The non-protein nitrogen was 150 mg. per cent; CO_2, 25 mEq./L.; chloride, 82 mEq./L.; sodium, 130.4 mEq./L.; potassium, 3.7 mEq./L.; blood type O, Rh positive. The patient continued to bleed after transfer to the medical service. She was given one unit of whole blood without reaction. Bleeding became minimal but persisted over the next few days. She continued to vomit and her blood pressure rose to 220/130. On the thirteenth hospital day the non-protein nitrogen was 134 mg. per cent; fasting blood sugar, 121 mg. per cent; sodium, 128 mEq./L.; potassium, 4.2 mEq./L.; chloride, 88 mEq./L.; CO_2, 22 mEq./L.; calcium, 9.0 mg. per cent; phosphorus, 9.1 mg. per cent; uric acid, 12.8 mg. per cent; creatinine, 13.5 mg. per cent; hematocrit, 21 per cent. She was given apresoline, reserpine, basaljel® and sodium chloride by mouth. On the fifteenth hospital day occasional emesis was again noted. The urine output remained low but showed a specific gravity of 1.010 and a negative reaction for protein. The patient passed a large clot per vaginum; pathologic examination of this specimen showed degenerated decidual cells and chorionic villi. On the sixteenth hospital day a repeat sodium was 127.6 mEq./L. The patient was given 240 cc. of 5 per cent sodium chloride by intravenous route following which the venous pressure rose from 170 to 190 mm. of saline. The urine output was 350 cc. On the seventeenth hospital day the non-protein nitrogen had risen to 170 mg. per cent and the serum sodium was 126.1 mEq./L. The following day the patient again received 5 per cent sodium chloride intravenously with a rise in venous pressure but no untoward symptoms or change in physical findings. The urinary output was again 350 cc. On the eighteenth hospital day some dependent edema developed. Two days later the urinary output was recorded as 25 cc. Minimal vaginal bleeding persisted as before and dependent edema was more prominent. A gallop rhythm was heard but the lungs were clear. Electrocardiogram showed sinus tachycardia and high voltage in the precordial leads suggestive of left ventricular enlargement. The hemoglobin was 6.2 gm. per cent and the hematocrit 19 per cent. The urine showed 3+ protein. The patient was given two red cell residue transfusions slowly without reaction and was placed on digitalis without subsidence of the gallop rhythm. On the twenty-first hospital day, the persistent emesis became blood-tinged. The patient was noted to have ascites, but the lungs were clear. Tachycardia persisted, but no gallop was heard. A repeat hematocrit was 27 per cent; hemoglobin, 9.1 gm. per cent; total protein, 5.2 gm. per cent; albumin, 3.6 gm. per cent; globulin, 1.6 gm. per cent; cholesterol, 205 mg. per cent. Hexamethonium was administered parenterally without any affect on the blood pressure which

averaged 230/140. On the twenty-second hospital day muscle twitches and a positive Chvostek sign were noted. A repeat hemoglobin was 8.2 gm. per cent. Uremic frost appeared and the edema progressed. The patient's weight had gradually risen to 147 pounds, although the fluid intake was minimal. A catheterized urine specimen showed a specific gravity of 1.011, 2+ protein, many white blood cells, a few red blood cells and occasional granular casts. On the twenty-third hospital day the blood calcium was 10.2 mg. per cent; phosphorus, 11.1 mg. per cent; alkaline phosphatase, 2.8 Bodansky units. The patient remained alert. She was anuric, and occasional muscle twitchings occurred. The cardiac rhythm was regular, the lungs remained clear, and the patient tolerated 500 cc. of 5 per cent sodium chloride intravenously without untoward effect. On the morning of the twenty-fourth hospital day the patient appeared more edematous but remained rational. The lungs were clear. She suddenly had a mild generalized convulsion while being bathed, became dyspneic and expired.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: This patient was a twenty-five year old Negro woman with severe hypertension which was discovered during her first pregnancy, two years prior to death. At the time of death she was uremic. First, I would like to mention the roentgenograms of the chest. Contrary to our usual procedure, we will not ask the radiologist to discuss these films since they showed no significant abnormalities. However, I assure you that the heart was not significantly enlarged. Dr. Smith, would you describe the electrocardiograms?

DR. JOHN SMITH: The electrocardiograms were not significantly altered regarding the complexes themselves. The T waves were upright in the three standard leads as well as in the precordial leads. There was evidence of left ventricular hypertrophy as judged by the so-called transitional zone of the precordial leads.

DR. REINHARD: The patient obviously had severe renal failure at the time of her death. The problem confronting us is what was the underlying kidney disease from which she suffered. Dr. Cordonnier, we were told that the patient had enuresis until age sixteen. I believe that in many instances enuresis is considered to be a psychosomatic disorder. However, this symptom can also be due to chronic infection in the urinary tract. Do you believe that the enuresis in this patient might have been due to a long-standing urinary tract infection?

DR. JUSTIN J. CORDONNIER: I suppose that is a possibility. However, there is nothing in her history to suggest that she had acute episodes of urinary tract disease during childhood. Enuresis is suggestive, of course, of a congenital malformation or urinary tract infection but I do not know whether one should attach too much importance to it.

DR. REINHARD: What percentage of patients with enuresis have congenital abnormalities of the kidney?

DR. CORDONNIER: In my opinion the incidence of organic disease in persons with enuresis is perhaps higher than is generally supposed. For that reason I believe all patients with enuresis should have a careful urologic evaluation.

DR. REINHARD: Later we will discuss the possible role of pyelonephritis in her renal disease. If the patient did have enuresis on the basis of a congenital anomaly of the urinary tract, might this anomaly have predisposed to a urinary tract infection?

DR. CORDONNIER: Definitely. Anything that will produce obstruction predisposes to infection.

DR. REINHARD: We may therefore consider the enuresis to be of possible significance in lending support to the idea that infection might have played an important part in the pathogenesis of the patient's hypertension. From early childhood until age twenty-three, when the patient had her first pregnancy, she had nocturia and polydypsia. Do these symptoms help us in arriving at a diagnosis?

DR. CORDONNIER: No, I do not believe so. Nocturia is significant and usually suggests urinary tract disease. Frequency during the day does not mean a great deal, but nocturia usually implies that there is organic disease present.

DR. REINHARD: What I had in mind was whether or not nocturia helps in the differential diagnosis between chronic glomerulonephritis and chronic pyelonephritis?

DR. CORDONNIER: No.

DR. REINHARD: The next problem I would like to consider is the effect of the first pregnancy on the underlying renal disease. Crabtree has reported that 80 per cent of all women have dilated ureters and renal pelves during pregnancy and for three or more months postpartum. I presume this is due to pressure of the uterus on the ureters, causing partial functional obstruc-

tion. If this be true, it is logical to surmise either that pregnancy might be a common cause of urinary tract infection or that it might be expected to cause an exacerbation of a pre-existing urinary tract infection. Indeed, the literature seems to support the concept that urinary tract infections are very common during and immediately after pregnancy, Crabtree found positive urine cultures in 25 per cent of a group of pregnant women who were otherwise normal and who had no symptoms of cystitis or of urinary tract infection. There are, in addition, many reports indicating a high incidence of symptoms suggesting urinary tract infection during the latter part of pregnancy and immediately after delivery. Would you comment on this relationship, Dr. Cordonnier?

DR. CORDONNIER: There are several theories as to the cause of ureteral dilatation during pregnancy which will not be discussed herein. Unquestionably, stasis in the upper urinary tract exists in a high percentage of such cases and, hence, the predisposition to urinary tract infection.

DR. REINHARD: Dr. Cordonnier, do you believe this patient had pyelonephritis as her basic underlying renal disease?

DR. CORDONNIER: I do not believe there is any way to tell whether or not this patient had obstructive uropathy, glomerulonephritis, or low grade chronic pyelonephritis. Any one of the three diseases would produce exactly the same symptoms. Nor does the fact that she had an exacerbation during her first pregnancy help. She had minimal pus cells in her urine after the first catheterization. The fact that pus and bacteria developed by the time of the second or third examination might indicate that she became infected from catheterization.

DR. REINHARD: Is it not true, however, that the concept that pyuria is consistently found in pyelonephritis is not necessarily correct? A patient could have severe long-standing chronic pyelonephritis and at least random urine specimens which show practically no pus cells.

DR. CORDONNIER: That is quite true. There may be complete atrophy of the kidney, with a normal urine, or there may be obstructive upper urinary tract disease which completely destroys the renal parenchyma with a consistently clear urine.

DR. REINHARD: I would now like to take up the problem of how long this patient had hypertension. The abstract implies that she was found to have hypertension during the seventh month of her first pregnancy. Actually, the note written by the obstetrical intern states that the patient was examined during the initial trimester of her first pregnancy and was told that her blood pressure was 180. Another point of interest is that an ophthalmology consultant described papilledema, a star figure of the macula, flame-shaped hemorrhages and exudates, and, in addition, marked attenuation of the arterioles, deep A-V nicking and copper wire streaks. One wonders whether these evidences of arteriolar sclerosis in a twenty-five year old woman might indicate hypertension of considerably more than two years' duration. Dr. Schroeder, do you believe this helps us any?

DR. HENRY A. SCHROEDER: No. I do not believe these changes help us determine how long hypertension was present. According to the latest figures I have seen* about 59 per cent of patients with pyelonephritis have hypertension, as do a similar number with chronic glomerulonephritis without azotemia. Neither the nature of the renal disease nor the stage to which hypertensive changes have progressed help us. This patient showed the clinical picture of malignant hypertension by the time we saw her, but the date of onset is unknown. If her blood pressure was elevated in the first trimester, the hypertension probably antedated the pregnancy.

A PHYSICIAN: I wonder if Dr. Schroeder believes that patients with pyelonephritis and hypertension tend to have higher levels of tension than do patients with chronic glomerulonephritis. The idea is often referred to in the literature especially in regard to the level of the diastolic pressure.

DR. SCHROEDER: No. I believe that the patient who has malignant hypertension and organic renal disease may have a diastolic pressure which is as high as if it were on the basis of nephrosclerosis. In other words, I do not believe that the organic renal disease, be it pyelonephritis or glomerulonephritis, influences the severe hypertensive state differently. The statistics which give the impression that the diastolic pressure is lower in glomerulonephritis include azotemic hypertension, in which state the pressure is usually lower than in the other two conditions; inclusion of these cases could skew the mean pressure values. Two factors

* Brod, Jan. Chronic Pyelonephritis. Prague, 1955. Statni Zdravotnicke Nakladatelstvi.

obviously must be present, the hypertensive diathesis and the kidney lesion, since nearly 40 per cent of patients with non-azotemic organic renal diseases do not have hypertension.

DR. REINHARD: The next question to be considered is whether or not the patient had toxemia of pregnancy during either of her two pregnancies. Dr. Woolf will you start the discussion by defining pre-eclampsia and eclampsia and by mentioning what features distinguish true toxemia of pregnancy from hypertension and proteinuria in the pregnant woman due to other causes?

DR. RALPH WOOLF: Pre-eclampsia and eclampsia are relatively common disorders usually seen during the latter half of pregnancy or early puerperium. They represent the same disorder, but of different severity, and to date are of unknown etiology. Pre-eclampsia and eclampsia are referred to as the acute toxemias of pregnancy. In general pre-eclampsia is said to exist if hypertension, generalized edema or proteinuria develops after the twenty-fourth week of pregnancy although the onset is usually after the thirtieth week. If convulsions and coma accompany these findings, the diagnosis of eclampsia may be made. We do not have sufficient information concerning this patient to support the diagnosis of a pure acute toxemia during her first pregnancy. She may have had a pre-existing hypertensive disorder with a superimposed acute toxemia of pregnancy. The problem of the postpartum convulsions merits some comment. Usually postpartum patients with eclampsia have the onset of convulsions within thirty hours from the time of delivery and rarely after the second day. From the history I question that this patient had an eclamptic seizure following her first delivery. The problem remains of an acute toxemia during her last pregnancy. Were a hydatidiform mole present toxemia might be considered in spite of the early stage of the patient's pregnancy. There is nothing in the record, however, to suggest a hydatidiform mole. I believe that we are dealing here with a normal early gestation complicated by severe hypertensive disease.

DR. REINHARD: Dr. Woolf, I do not believe it is clear from your discussion whether eclampsia or pre-eclampsia really constitute entities distinct from the same manifestations occurring in a woman with pre-existing renal disease and hypertension. How do you distinguish these two conditions?

DR. WOOLF: I believe that the acute toxemias constitute a distinct entity. To distinguish which of the two disorders might be responsible one can usually rely upon the criterion of whether the findings were present before or after the twenty-fourth week of pregnancy. If the patient is seen for the first time after the twenty-fourth week, it may be impossible to determine the etiology of the findings unless a reliable history is obtained or physical evidence of chronicity, such as chronic hypertensive eye ground changes, is apparent. One should always bear in mind that acute toxemia of pregnancy frequently is superimposed upon chronic hypertensive disease during the last trimester of pregnancy which adds to the difficulty of arriving at an accurate diagnosis. In general, I believe that the most reliable appraisal of the situation in previously unknown patients can only be made in retrospect, as advised by Dieckmann, by a thorough evaluation of the patient three to six months after delivery. Until recently there has been a strong belief in many quarters that the acute toxemias of pregnancy cause persistent hypertension and chronic renal lesions. This view had been supported particularly by Chesley and E. Page. Dieckmann,on the other hand, has always maintained that the acute toxemias of pregnancy do not cause permanent hypertension or renal damage as evidenced by negative follow-up studies.

DR. REINHARD: In summary, then, do you believe this patient did or did not have toxemia of pregnancy? I assume from your remarks that you are very skeptical of this diagnosis.

DR. WOOLF: I do not believe she had toxemia of pregnancy.

DR. REINHARD: Before leaving the subject of toxemia of pregnancy we might consider whether or not pre-existing pyelonephritis and hypertension predispose true toxemia of pregnancy to develop. Dexter and Weiss some years ago stated that acute pyelonephritis is not a predisposing factor to the development of toxemia but that patients with chronic pyelonephritis and associated hypertension with low kidney reserve do have a definite predisposition to develop toxemia. Are these observations valid or do the patients with chronic pyelonephritis merely have an exacerbation of their chronic renal disease and hypertension?

DR. WOOLF: I believe their observations are quite valid. Also, patients with chronic hypertensive vascular disease are prone to develop a superimposed acute toxemia of pregnancy. The

incidence of acute toxemia in chronic hypertensives has been reported to vary from at least 25 per cent to as high as 80 per cent in different series.

DR. REINHARD: It has been stated that the funduscopic findings in toxemia are different from those seen in severe hypertension due to other causes. Do you believe that this distinction can be made, Dr. Schroeder?

DR. SCHROEDER: I cannot make the distinction between hemorrhagic and exudative lesions in diabetic retinopathy and similar ones in hypertensive retinopathy, much less toxemic retinopathy. There are, however, suggestive findings. If one observes the "retinal sheen," which is probably the result of diffuse edema of the retina, it can be assumed that the patient has some sort of water retention or is exuding serum into the retina. If one notes such evidence of edema, one might make the distinction between the retinopathy of uremia without much hypertension and retinopathy which could be due either to malignant hypertension or, more commonly, to toxemia of pregnancy. The presence of waxy exudates, which appear to have been there a long time and look like scar tissue, would indicate that the patient has had severe hypertension antedating the pregnancy. I do not believe one can tell the difference in acute episodes of malignant hypertension, whether associated with toxemia or renal disease, unless the older lesions are present.

DR. REINHARD: Dr. Schroeder, do you believe we must consider any mechanism other than renal disease as the underlying cause of the hypertension in this patient?

DR. SCHROEDER: No, I believe we are perfectly safe on that score. She had a family history of hypertension which would go with it. May I disagree with Dr. Cordonnier's conservative statement? We have a pretty good case for pyelonephritis, possibly with a congenital anomaly, from the small clues in the protocol. There was enuresis. The urine showed white blood cells in clumps, but no albuminuria. Approximately 30 per cent of people with pyelonephritis do not have albuminuria after the kidneys are scarred. There was slow development of the uremia, which probably goes along better with pyelonephritis than with glomerulonephritis. Since pyelonephritis accounts for about 36 per cent of all cases of uremia, I believe pyelonephritis is a good bet in the absence of a more specific history. Of course, nephrosclerosis could be superimposed on the pathologic process.

DR. CORDONNIER: I certainly did not mean to give the impression that I do not believe pyelonephritis could account for the patient's symptomatology. I agree with Dr. Schroeder completely.

DR. REINHARD: Dr. Loeb, in practically all patients with renal failure and chronic azotemia significant anemia develops at some time. I wonder if you would comment briefly on the pathogenesis of this type of anemia. Would you also mention the relative significance of the severity of the azotemia and the duration of the azotemia in the production of the anemia?

DR. VIRGIL LOEB: It has been shown that the anemia of most patients with chronic renal disease is related to several factors. A decreased production of red blood cells may be demonstrated by measuring the utilization of radioactive iron or hemoglobin synthesis. In patients with severe azotemia and a lowered red cell count the incorporation of iron into hemoglobin is decreased below that of normal persons. This may be taken to indicate that there is defective erythrocyte production or at least impaired formation of hemoglobin. On the other hand there is good evidence that in certain cases there is an accelerated destruction of red blood cells as demonstrated by measuring the survival time of transfused cells.* In conjunction with your question about the relation of the severity of the azotemia to the anemia, I might mention that in our own experience those cases in which there was a significant hemolytic component to the anemia all had levels of non-protein nitrogen above 100 mg. per cent. The shortened red cell survival time appears to be due to an extracorpuscular mechanism. It has been shown that when normal red blood cells are transfused into patients with the anemia of renal disease, the survival of these cells may be grossly deficient; however, if one takes red cells from patients with this type of anemia and transfuses them into normal persons, such erythrocytes have a normal survival time. With respect to the bone marrow of these patients, it is difficult to obtain much of an impression of the pathogenesis of the anemia from the morphology. Limarzi has studied a large number of patients with nephritis and has found very little correlation between the appearance of the bone marrow and the severity of the anemia until the non-protein nitrogen reaches a level of 150 mg. per cent or

* Loge, J. P., Lange, R. D. and Moore, C. V. *J. Clin. Investigation*, 29: 830, 1950.

above; in these cases the marrow is generally hypocellular. I believe, in summary, that one may say that in patients with renal disease and severe azotemia, the anemia is due to some factor or factors which suppress red blood cell production and also shorten the life span of the circulating erythrocytes.

DR. REINHARD: This patient had various bleeding manifestations including hemorrhages of the fundi, postabortion vaginal bleeding, hematuria and blood-tinged emesis. Obviously, all of these manifestations could be related to the vascular phenomena associated with severe hypertensive cardiovascular disease and uremia. We do not have to postulate a defect in the coagulation mechanism. However, I believe it would be interesting to discuss briefly the coagulation disturbances that can occur postpartum or following abortion as well as in association with toxemia of pregnancy. Dr. Matheson, a visitor from Johns Hopkins Medical School who has done a good deal of work in this field, will discuss the problem for us.

DR. WILBUR MATHESON: I do not believe that, in the average patient with an elevated non-protein nitrogen who has bleeding, one need consider any basic coagulation defect. There was no evidence here of thrombocytopenia. In patients with bleeding defects due to fibrinogen deficiency associated with pregnancy, particularly abruptio placentae, septic abortion, or with fetal death in utero, this deficiency has been rather rapidly corrected after the fetus has been delivered. It would seem that since the patient had aborted, her vaginal bleeding might well be a manifestation of the uremic tendency.

DR. REINHARD: You believe, then, that there was no reason to suspect any coagulation defect.

DR. MATHESON: I would think not.

DR. REINHARD: Dr. Schroeder, this patient was in three different hospitals during her terminal illness, which might have accounted for the lack of continuity in the therapy of her hypertension. I wonder if you would tell us, however, how you would have managed her hypertension had she been under your care throughout her illness.

DR. SCHROEDER: The most one can do when the non-protein nitrogen is elevated is to push the one drug which seems to act on the kidney by dilating its vessels, and that would be hydralazine. Of course, those renal arteries and arterioles that are constricted functionally may be dilated, but those constricted organically by scar tissue and fibrosis will not. It has been our experience that patients with a non-protein nitrogen over 60 mg. per cent by the Somogyi-zinc method used in Barnes Hospital have a poor prognosis. Only one such patient is alive after two years. Patients with non-protein nitrogen under that level do fairly well.

DR. REINHARD: Dr. Reiss, would you discuss the electrolyte changes that occurred in this patient.

DR. ERIC REISS: The serum electrolyte changes in this patient are fairly characteristic of far advanced renal insufficiency. There are a few points, however, which deserve comment. In far advanced renal insufficiency, one would expect more acidosis than this patient had. The carbon dioxide combining power was never less than 22 mEq./L. The serum potassium concentration did not increase until very late in the course of the disease. In fact, it remained normal with a urinary output of only 350 cc. per twenty-four hours. Terminally, the severe oliguria was associated with a serum potassium increase. The hyponatremia and hypochloremia raise several questions. This patient may have been salt depleted before she came to the hospital because of persistent vomiting. We cannot exclude this possibility. The clinical response to salt therapy was not impressive. A second possibility which should be borne in mind is that the patient was excreting large amounts of salt. I consider this very unlikely, but it is a possibility. I believe that the best explanation for the hyponatremia and hypochloremia is dilution of the extracellular fluid with water, which would suggest that the patient received a disproportionately large amount of water in relation to salt and was unable to excrete the excess water. In support of this idea, note that the weight increased from 133 pounds on the thirteenth day to 147 pounds on the twenty-second day, that the water intake was relatively high, and that the salt intake was low.

DR. REINHARD: How do you account for the fact that the patient received a large amount of sodium chloride on the seventeenth and eighteenth hospital days with only a transient effect on the serum sodium level?

DR. REISS: At first glance, 240 cc. of a 5 per cent sodium chloride solution appears to be a large amount of salt. However, this volume actually represents only about 200 mEq. of sodium and of chloride. At the same time the

patient received much water and had a urinary output of only 350 cc. These data fit the dilutional hypothesis nicely.

DR. REINHARD: Dr. Massie, do you have anything to add?

DR. EDWARD MASSIE: I would like to ask Dr. Schroeder what percentage of cases of malignant hypertension are secondary to glomerulonephritis or pyelonephritis and what percentage are secondary to nephrosclerosis. It is my belief that in malignant hypertension, the majority of cases probably have primary vascular disease.

DR. REINHARD: We will have to qualify that question by asking Dr. Schroeder what would the percentages be in young women.

DR. SCHROEDER: If you consider people under forty, which is the only group I have collected,* eighty of 250 had some sort of organic renal disease, half of those showed exudative retinitis and 68 per cent of those who died went into the malignant phase of hypertension. In other words, if you have organic renal disease and hypertension develops, the chances of entering the malignant phase are about 50:50. At twenty-five, with possible renal disease dating from childhood, I think the chances of hypertension being on an organic renal basis rather than on a primary vascular disease are excellent. So-called primary nephrosclerosis, which is not primary but secondary malignant nephrosclerosis caused by the hypertensive state, usually occurs in the thirties or forties, although it may be seen in later decades, even in patients as old as seventy. One further point: Dr. Saphir reported three years ago† that 98 per cent of cases of malignant hypertension coming to autopsy had signs of pyelonephritis when examined carefully. He called this condition "pyelonephritis lenta."

DR. REINHARD: Dr. Massie, I would take it from your remarks that you would not be willing to accept the idea that this patient had renal disease going back to childhood. Of course, we have no positive evidence for that. Do you believe that her renal lesion is of more recent origin?

DR. MASSIE: Yes, I believe that it is secondary to the hypertension.

DR. MELVIN GOLDMAN: I would like to ask Dr. Schroeder a question because I am not certain what he meant when he said that almost all persons with hypertension with non-protein nitrogen of over 60 mg. per cent did not do well with any antihypertensive therapy. To which group of patients is he referring?

DR. SCHROEDER: Practically all of our malignant hypertensive patients with azotemia who had an initial non-protein nitrogen above 60 by the Somogyi-zinc method in the absence of heart failure have not done well. We have only one of twenty patients alive after seventeen months. Another patient with a non-protein nitrogen of 130 left the hospital with a non-protein nitrogen of 42; he has lived so far three months. Most of the others either did not leave the hospital or died within the first six months following discharge. Those with an initial non-protein nitrogen of 60 or below, which seems to be the breaking point, have on the whole done pretty well, twenty-seven of forty-six being alive.

DR. REINHARD: Would this be true if the azotemia were due to a process which could be corrected, such as an obstruction?

DR. SCHROEDER: No. None of these patients, however, has been operated upon. We now have twenty-seven azotemic or formerly azotemic malignant hypertensive patients alive after an average duration of twenty-eight months of treatment who initially manifested non-protein nitrogens from 30 to 60 mg. per cent. Without treatment their prognosis would have been uniformly poor.

DR. REINHARD: My concept of the sequence of events in this case may be summarized as follows: I believe this patient did have a chronic renal disease going back a good many years before her first pregnancy. I am inclined to believe that this is in the nature of a urinary tract infection. During her first pregnancy she had an exacerbation of her pyelonephritis and hypertension. In the initial stages of her second pregnancy a further intensification of the process occurred and the patient went into the phase of malignant hypertension. We certainly cannot exclude the possibility of malignant nephrosclerosis or that the underlying renal disease might be glomerulonephritis, but I am inclined to think that pyelonephritis is a more likely explanation.

PATHOLOGIC DISCUSSION

DR. JAMES C. HARKIN: The principal anatomic findings were diffuse severe arterial and arteriolar sclerosis with extensive necrosis of

* SCHROEDER, H. and STEELE, J. M. *Arch. Int. Med.*, 68: 261, 1941.

† SAPHIR, O. and TAYLOR, B. *Ann. Int. Med.*, 36: 1017, 1952.

arterioles, or in other words the morphologic stigmas associated with malignant essential hypertension.

The kidneys weighed 130 and 120 gm. and had a finely granular surface. There were scattered punctate hemorrhages corresponding to the regions of intratubular hemorrhage identified microscopically. On section the cortex was not reduced in thickness. The major branches of the renal artery and the arcuate arteries were normal. Every interlobular artery examined was the seat of a striking intimal thickening or proliferation. (Fig. 1.) In some of these arteries the tiny lumen was completely occluded by a fibrin thrombus. The afferent arterioles were thickened and hyalinized. Isolated arterioles had walls that were smudged and intensely eosinophilic, characteristic of arteriolar necrosis. If such an arteriole was the afferent vessel of a glomerulus, the necrotic process extended on into the tuft. (Fig. 2.) Some glomeruli were reduced to hyalinized scars. However, the majority had no structural abnormality aside from an equivocal thickening of the basement membranes. In the zones adjacent to scarred glomeruli some tubules were small and others dilated with colloid casts. A small amount of fat was present in a few tubular epithelial cells. An additional diagnosis of focal acute pyelonephritis was made, based on the finding of an interstitial infiltration of polymorphonuclear leukocytes adjacent to tubules filled with cellular casts.

Thickening of arterial walls was also present in the pancreas and brain. (Fig. 3.) In the pancreas, adrenal cortex, ovary and uterine cervix there was necrosis of arterioles. (Fig. 4.)

The heart was enlarged (410 gm.) and dilated. Anasarca, ascites (3,000 ml.) and hydrothorax (750 ml.) were present.

The uterus had not yet undergone involution. The endometrium was the seat of focal necrosis and hemorrhage with acute inflammation. The adjacent endometrial stroma was focally hyalinized, while the glandular epithelium was in a stage of non-uniform proliferation. These changes would be compatible with the recent abortion.

In the adrenal gland changes had developed similar to those that occur in experimental animals with hyponatremia on a low sodium diet, a situation somewhat analogous to that present in the patient. These alterations consisted of thickening of the zona glomerulosa with depletion of lipid in the outer portion of the zone and prominent lipid droplets in the inner portion. (Fig. 5.) Another change which occurs in hyponatremic animals is increased granulation of the cells of the juxtaglomerular complex.[2] Figure 6 illustrates the marked granularity of the juxtaglomerular cells in this case. However, it should be appreciated that three processes, all associated with hyperplasia of juxtaglomerular cells, were present in this case: hyponatremia, hypertension and toxemia of pregnancy.

An interpretation of the renal vascular lesions as changes resulting from toxemia of pregnancy would seem unwarranted. In toxemia of pregnancy without pre-existent renal disease the anatomic lesions are minimal or equivocal, and any changes which occur appear to be reversable. The present case would seem to be most adequately considered as one of malignant essential hypertension in a young Negress. The prominent proliferative arterial lesion is more frequently associated with malignant hypertension when it occurs in young people, particularly those of the Negro race.

DISCUSSION AFTER PATHOLOGY PRESENTATION

DR. REINHARD: I am certain that you are all aware of the fact that the terminal events in malignant hypertension very often obscure the origin of the hypertension. I do not believe that Dr. Schroeder and I have to apologize the least bit for having guessed that the original lesion was a pyelonephritis. Certainly that could have accounted for all the findings in this case. All one can do in a clinico-pathologic conference is to make an informed guess on the basis of statistical probability. I am still inclined to think that our diagnosis was the best statistical probability, but Dr. Massie was correct as far as the actual diagnosis was concerned. Do you have anything further to add, Dr. Massie?

DR. MASSIE: My information came from a study carried out some years ago at the Peter Bent Brigham Hospital in which we found that patients who had the highest pressures and were in the younger age group more often had malignant hypertension on the basis of primary vascular disease than as a result of primary nephritis.

DR. REINHARD: Do you accept this as valid observation, Dr. Schroeder?

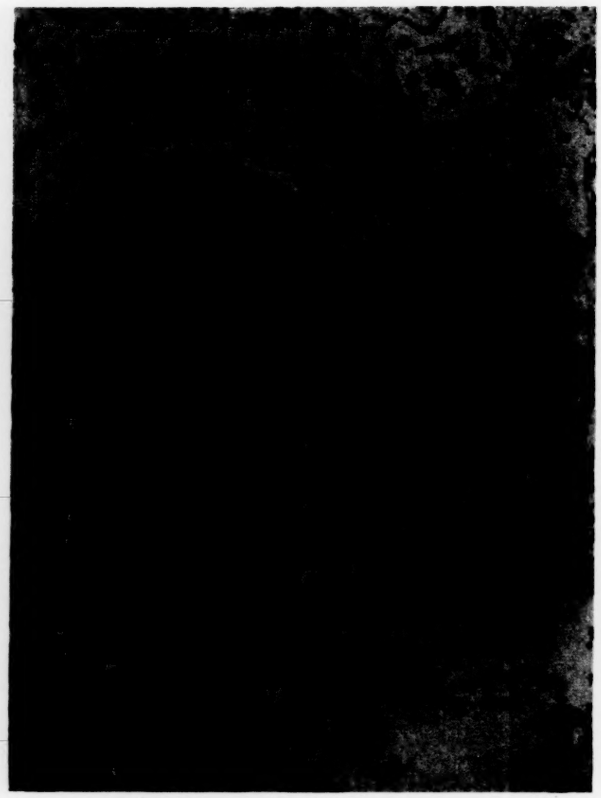


FIG. 1. Arteriolar and glomerular necrosis; hematoxylin and eosin, approximately × 100.

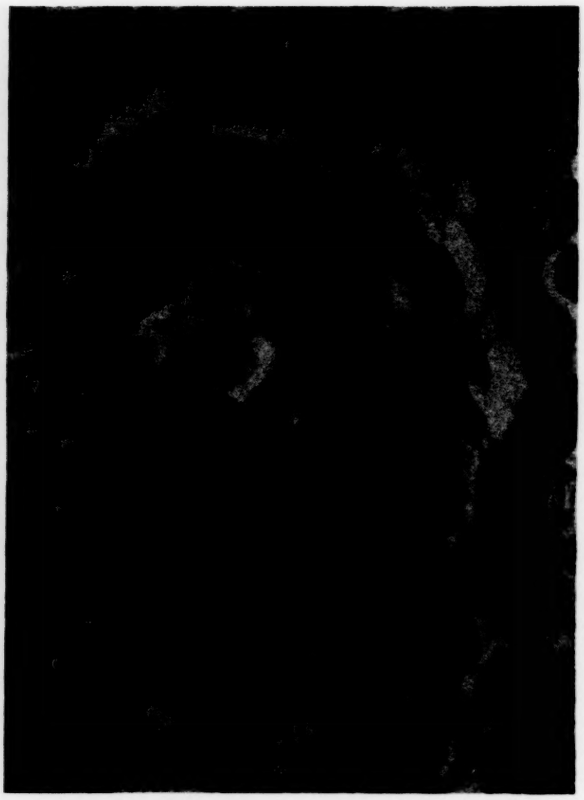


FIG. 2. Arteriolar necrosis, adrenal capsule; hematoxylin and eosin, approximately × 420.

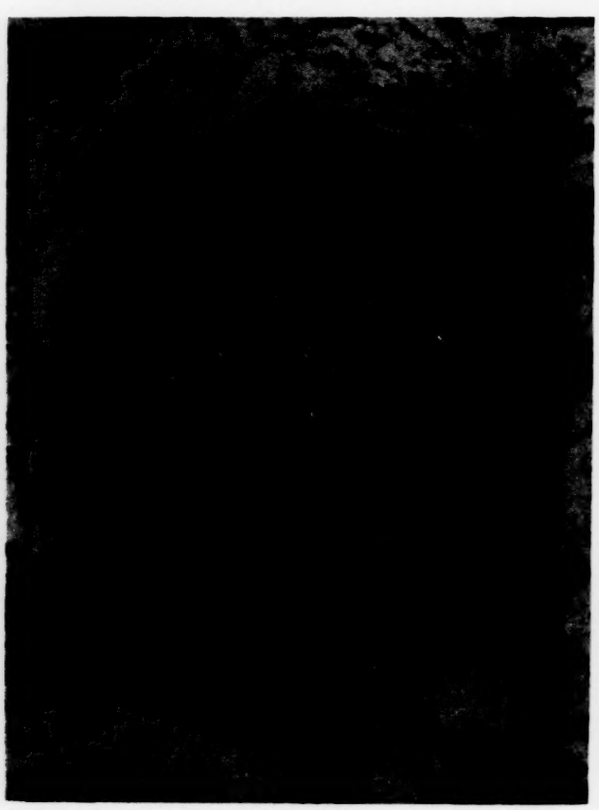


FIG. 3. Arteriosclerosis, interlobular artery, kidney; Verhoeff-van Gieson, approximately × 250.

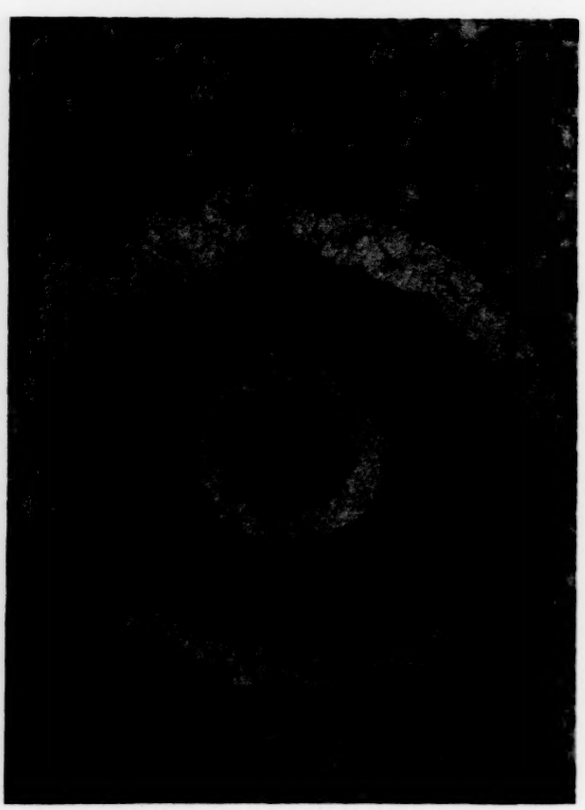


FIG. 4. Cerebral arteriosclerosis; hematoxylin and eosin, approximately × 250.

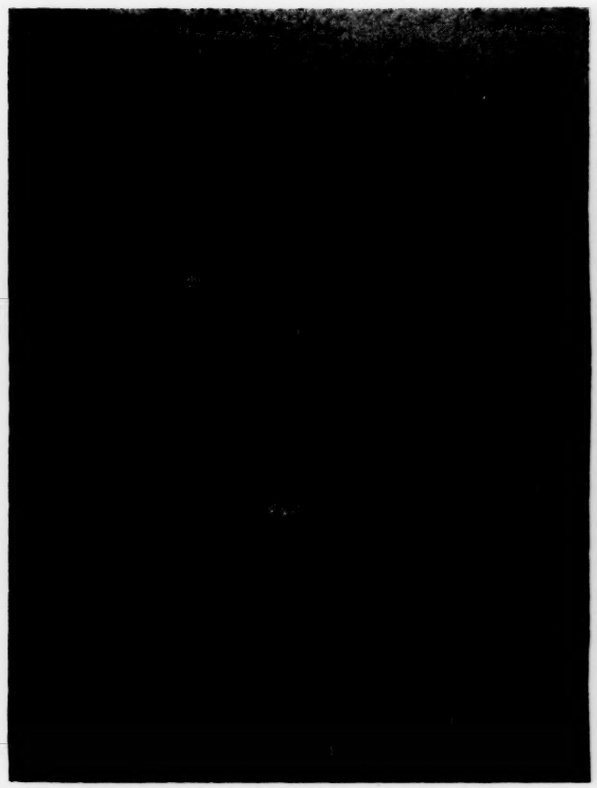


FIG. 5. Adrenal, lipid depletion of outer portion of the zona glomerulosa; oil red 0 and light green (Wilson), approximately × 42.

FIG. 6. Kidney, juxtaglomerular cells; Bowie's neutral stain, approximately × 970. Arrow indicates clump of granules.

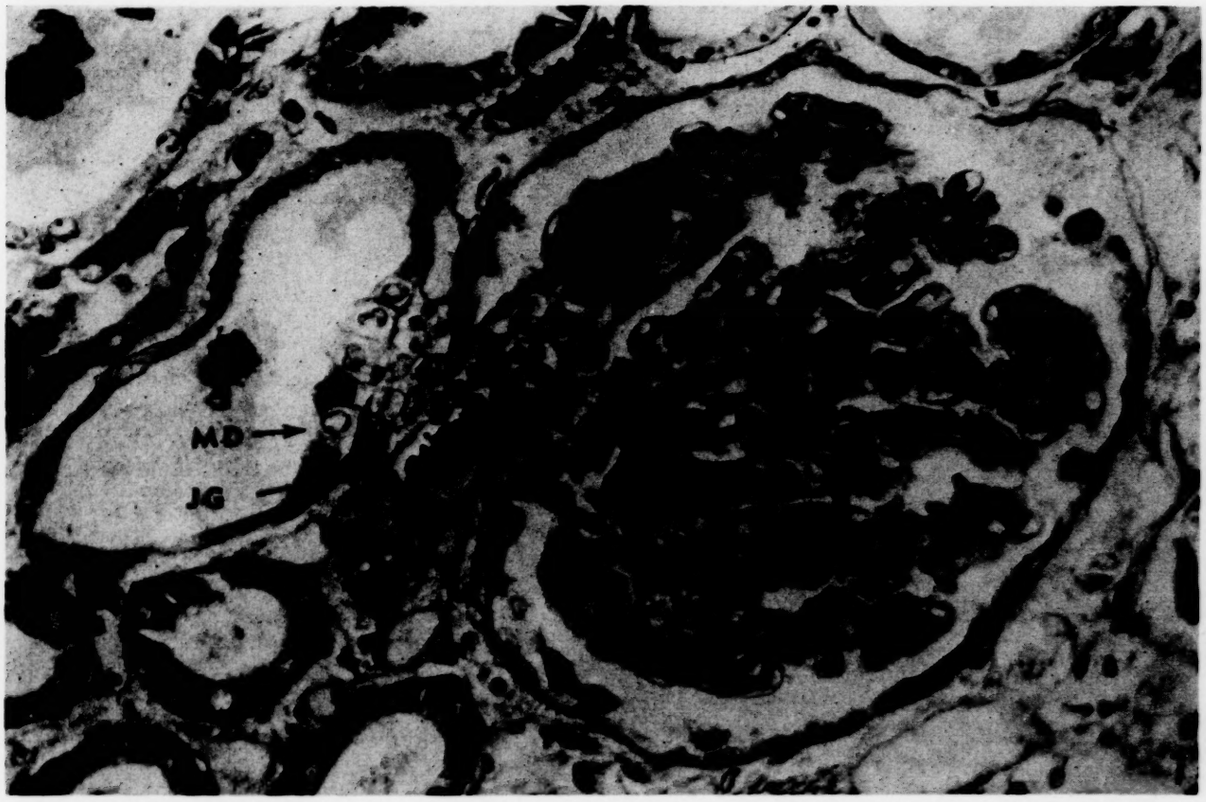


FIG. 7. Kidney, granular juxtaglomerular cell indicated at JG, macula densa at MD; Bowie's neutral stain, approximately × 250.

DR. SCHROEDER: I am a little stubborn about that. I do believe that we should have paid more attention to the fact that the patient was a Negro. Malignant nephrosclerosis with a violent, rapid, downhill course is frequent in young Negro women. On the other hand, for ten years I have been trying to determine which of the three pathologic processes is present when you see a patient in uremia and my batting average is usually less than one in three.

Acknowledgment: Illustrations were made by the Department of Illustrations, Washington University School of Medicine.

BIBLIOGRAPHY

DEANE, H. W., SHAW, J. H. and GREEP, R. O. The effect of altered sodium or potassium intake on the width and cytochemistry of the zona glomerulosa of the rat's adrenal cortex. *Endocrinology*, 43: 133, 1948.

HARTROFT, P. M. and HARTROFT, W. S. Studies on renal juxta-glomerular cells. I. Variations produced by sodium chloride and desoxycorticosterone acetate *J. Exper. Med.*, 97: 415, 1953.

Research Society Abstracts

Southern Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE TENTH ANNUAL MEETING, NEW ORLEANS, LOUISIANA, JANUARY 21, 1956

STEROID THERAPY OF CONGENITAL AREGENERATIVE ANEMIA. *W. R. Arrowsmith and A. Segaloff.** Dept. Medicine, Tulane University and Ochsner Clinic, New Orleans, La.

A three month old infant with aregenerative anemia who had previously received multiple transfusions and hematinics was seen. Cortisone produced a gradually increasing peripheral macrocytosis and the bone marrow showed hyperplasia of the red cell series with maturation arrest. Vitamin B_{12} and folic acid therapy were then given with marked hematologic response. Relapse occurred when steroid therapy alone was stopped. Splenectomy was ineffective. Three and one-half years of remission without transfusion were obtained with steroids alone. Development during this time had been essentially normal; apprehension regarding the effect of continuous steroid therapy on development proved unfounded. A second infant, six months of age, with the same disorder was seen and has been maintained for two years on steroid therapy, with a satisfactory blood count. The only transfusion needed during this period was when steroid therapy had been interrupted. Two similar older children showed definite but incomplete responses to steroid therapy. A thirteen year old boy has required fewer transfusions while on steroids than at any previous time. These four children are the only ones with this disease we have seen here. The natural course of the disease appears to have been altered by steroid therapy in all four patients.

HEMODIALYSIS: AN EFFECTIVE THERAPY FOR ACUTE BARBITURATE POISONING. *L. B. Berman, G. E. Schreiner,* H. Jeghers** and A. Pallotta.* Dept. Medicine, Georgetown University Medical Center, Washington, D. C.

Acute barbiturate poisoning produces a reported annual death toll of 1,000 persons in the United States and is responsible for an estimated 15,000 hospital admissions. Only supportive measures and the use of analeptics, the value of which is controversial, have been available as therapy. In severe cases mortality and morbidity rise with the condition is complicated by prolonged coma. Experimental evidence in both animals and human subjects suggests that a more direct clinical approach is feasible by removal of the barbiturate from the body through hemodialysis. This is clinically practical with the currently available models of the "artificial kidney."

The present study concerns an analysis of twenty-six patients admitted to Georgetown Hospital for acute barbiturate poisoning over a two-year period. Details of supportive management are presented on seven patients in whom accurate measurements of blood barbiturate level were obtained. Particular emphasis is given to eight patients who were selected for dialysis because of the severity of the clinical picture. These include poisoning with phenobarbital, barbital, nembutal,® amytal,® seconal® and mixtures. One patient ingested 664 mg./kg. of phenobarbital and had a peak blood concentration of 29.3 mg. per cent; dialysis on three occasions removed 9.3 gm. of phenobarbital. Another patient ingested sufficient tuinal® to achieve a blood level of 10.5 mg. per cent nine hours after ingestion; dialysis produced striking clinical improvement with removal of 12 per cent of the ingested dose. These are among the highest blood levels ever recorded for these respective types. In seven of eight patients, dialysis produced lowering of blood barbiturate level and discernible clinical improvement.

The clinical course of these patients and the efficiency of dialysis with respect to type of drug, blood concentration, elapsed time from ingestion, underlying disease and technical aspects of the dialysis procedure are discussed. Dialysis appears to be an effective and sometimes lifesaving measure for the specific treatment of acute

* Throughout these abstracts asterisk designates member of the Southern Society for Clinical Research.

barbiturate poisoning which should be regarded as a prime medical emergency.

PRODUCTION OF ACUTE PULMONARY VASCULAR ENGORGEMENT IN MAN: ITS EFFECT ON COMPLIANCE AND OCCURRENCE OF COMPENSATORY RESPONSES OF CIRCULATION. *S. O. Bondurant and J. B. Hickam.** Dept. Medicine, Duke University School of Medicine, Durham, N. C.

In congestive heart failure the lungs are stiff and dyspnea is partially caused by this condition. To investigate the effect of acute vascular congestion on stiffness of the lungs, observations have been made in normal subjects during inflation of a G-suit. Pulmonary compliance and central venous pressure were measured and changes in pulmonary vascular density were followed by x-ray. Eleven subjects were studied. With suit inflation (2–3 psi) central venous pressure increased immediately by a mean of 26.5 ± 9.0 cm. H_2O coincident with marked increase in pulmonary vascular density by x-ray. Pulmonary compliance decreased immediately from a mean of .218 ± .035 L./cm. H_2O to a mean of .100 ± .033 L./cm. H_2O ($p < .001$). These findings demonstrate that acute pulmonary congestion can produce in normal subjects reversible compliance changes comparable to those of severe congestive failure.

Development of rapid compensatory changes in the circulation became apparent as suit pressure was maintained. These changes began almost immediately and within sixty seconds central venous pressure had decreased by 5.3 ± 2.8 cm. H_2O ($p < .001$). Compliance rose from .108 ± .034 L./cm. H_2O to .144 ± .049 L./cm. H_2O and radiographic density decreased markedly. These changes apparently represent the action of a normal adaptive mechanism which tends to oppose extreme central vascular engorgement presumably by shifting blood into the periphery. This response obviously can have considerable protective value in circulatory stress imposed by more familiar means.

THE MUCOPROTEIN-MUCOPOLYSACCHARIDE MATRIX OF URINARY CALCULI; BIOCHEMICAL, HISTOCHEMICAL AND MICROSCOPIC STUDIES. *W. H. Boyce** *and N. M. Sulkin.* Depts. Urology and Anatomy, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

Calculi were decalcified with ethylenediaminetetraacetate and the matrix recovered by ultrafiltration. The average quantity of matrix from 500 calculi was 2.53 per cent (weight/weight) and the range was from 1.71 to 3.22 per cent. Matrices of sixty-four single calculi were recovered as casts of the original stones by formalin fixation and decalcification. Microscopic study revealed laminations of fibrils with intervening "ground" substance. Parallel orientation of the fibrils was noted which stained brilliantly and gave a positive reaction to the periodate Schiff test, indicating the presence of neutral mucoprotein. Calcium salts were deposited in the ground substance with alignment along the borders of the mucoprotein fibrils. The decalcified matrix was orthochromatic with aqueous toluidine blue, but uncalcified ground substance was metachromatic, indicating acid conjugated mucopolysaccharide. The mucoprotein could not be solubilized without degradation, but a soluble mucopolysaccharide recovered from the matrix contained (weight/weight): carbon 56.33, hydrogen 7.88, nitrogen 10.29, sulfur 0.71, phosphorus 0.70, calcium 0.51 and ash as sulfate 6.03. It contained 8.16 per cent hexose and 5.4 per cent hexosamine. Tests for hexuronic acid and lipids gave negative results, but results were positive for ninhydrin. At pH 8.6 it was electrophoretically homogeneous with a mobility of -5.61×10^{-5} cm.^{2} per volt second. The matrix is of similar composition in all calicigerous stones regardless of inorganic composition of the crystals.

RELATIONSHIP OF BACTERIAL SPECIES TO THE PATHOGENESIS OF HEMATOGENOUS PYELONEPHRITIS. *A. Braude,** *A. Shapiro and J. Siemienski.* Dept. Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex.

Although several bacterial species may produce pyelonephritis, their specific role in the pathogenesis is obscure because human kidneys are examined rarely during the early stages of the disease. Therefore, an experimental model of human hematogenous pyelonephritis, which combines renal massage (through the intact abdominal wall) with intracardiac injection of bacteria (*J. Clin. Investigation*, 34: 1489), was employed to study variations in pathogenesis with different bacterial species. During a period of six weeks after inoculation, the severest pyelonephritis was observed with Proteus mirabilis, which also induced lithiasis of the kidney (NH_4MgPO_4 stones) in three of fourteen rats and mild hypertension in three. Marked destruction also occurred with Escherichia coli and Pseudomonas aeruginosa; much less destruction

occurred with Streptococcus zymogenes. Yet renal cultures at six weeks yielded far heavier growth of St. zymogenes than of Esch. coli or Ps. aeruginosa. Existing pyelonephritis due to Esch. coli usually prevented superinfection by Str. zymogenes, and intense cellular infiltration often persisted after infection by gram-negative organisms had disappeared.

These results suggest that, although gram-negative pathogens disappear more rapidly from the kidney, they are more destructive than gram-positive organisms and their inflammatory reaction persists after infection subsides.

STUDY OF THE VENOMOTOR STATE IN A SHORT INTACT VENOUS SEGMENT OF THE FOREARM OF MAN. *G. E. Burch* and M. Murtadha.* Dept. Medicine, Tulane University School of Medicine and Charity Hospital, New Orleans, La.

A venous segment was isolated by brass wedges from the general circulation, and the pressure within was followed by means of the phlebomanometer with volume constant in the segment. The following factors increased the venomotor tone in the segment: thinking, deep inspiration, psychic and emotional disturbances, mathematic calculation and noradrenalin. Segmental pressure was reduced by contralateral intravenous administration of hexamethonium and stroking the skin over the segmental vein. Pressure over the hepatic area in subjects with chronic congestive heart failure increased segmental venous pressure, whereas contralateral intravenously administered hexamethonium reduced it, supporting the concept of increased venous tone in the forearm vein in congestive failure. Occasionally spontaneous spasm in the isolated segment raised pressure to 600 mm. of H_2O. Noradrenalin in the segment increased pressure to 600 or more mm. of H_2O. Procaine locally blocked segmental venoconstriction produced by deep inspiration. Segmental veins showed spontaneous rhythmic contractions like the alpha and beta waves described in the digits of man.

This segment is an excellent simple preparation for studying venous phenomena in superficial intact veins. The studies show the tone of the veins in the arm to be elevated in congestive heart failure.

DETERMINATIONS OF PLASMA: WHOLE BLOOD RATIOS AND VOLUMES BY SIMULTANEOUS COUNTING OF I-131 AND CR-51. *W. H. Cargill,* A. P. Murphy and J. C. Coberly.* V. A. Hospital and Emory University School of Medicine, Atlanta, Ga.

Pulse height analysis permits the counting of I-131 and Cr-51 in the same blood sample. Following intravenous injection of I-131 labeled albumin and Cr-51 labeled erythrocytes the concentration of these isotopes was determined in fifty-seven samples of blood from ten normal subjects and the blood volumes calculated. The following values for whole blood volume were obtained (cc./kg.): mean 61.8, range 47.7 to 74.1, standard deviation ± 5.6. Thirty-five determinations in eight patients with moderate to severe untreated congestive heart failure revealed the following values: whole blood volume, mean 71.7, range 48.6 to 116.1, standard deviation $\pm$ 19.8; plasma volume, mean 40.8, range 21.6 to 63.4, standard deviation ± 11.8. The plasma: whole blood ratio was calculated from the formula:

$$\text{CVH} = 1 - \frac{\text{Cts. I-131/cc. whole blood}}{\text{Cts. I-131/cc. plasma}}$$

and compared with the hematocrit reading. Two hundred and eighty-three determinations of the ratio $\frac{\text{CVH}}{\text{hematocrit reading}}$ revealed a mean value of 1.02, standard deviation ± 0.12, standard deviation of the mean $\pm .007$, indicating that trapped plasma does not contribute to the hematocrit reading and correction factors are unnecessary.

EFFECTS OF RELAXIN IN TREATMENT OF SCLERODERMA. *G. G. Casten, R. J. Boucek, N. L. Noble and T. M. Scotti* (introduced by T. R. Harrison*). Research Laboratories of Miami Heart Institute and University of Miami School of Medicine, Miami, Fla.

Relaxin, a peptide-like material secreted by the mammalian ovary during pregnancy, is known to produce a change in the ground substance of connective tissue in the pubic symphysis. The present study reveals marked changes in the histologic picture of rat connective tissue obtained by the sponge biopsy technic. This is characterized by loosening of collagen fibers and appearance of wide areas of myxomatous-like tissue. Chronic administration of relaxin produces a loosening of the skin of laboratory animals and a lowering of the collagen concentration of the rat sponge connective tissue biopsy specimen.

These results led to the use of relaxin in the treatment of scleroderma, a generalized connective tissue disorder that affects predominately collagen. During the past ten months, twelve patients with this disease and three patients with Raynaud's disease have been treated continuously with varying degrees of clinical improvement by (1) marked increase in skin elasticity and pliability, (2) improvement or complete cessation of Raynaud's phenomena, (3) healing of chronic trophic ulcers, (4) slight improvement in esophageal symptoms and (5) no appreciable change in advanced sclerodactylia. Our experience indicates that relaxin delays progression and tends to produce a reversion towards normal of certain manifestations of scleroderma. Continued daily intramuscular administration in doses of 20 to 40 mg. is necessary as prompt relapse occurs when treatment is stopped. No toxic side effects have been observed.

THE VALUE OF OXIMETRIC DYE CURVES IN THE IDENTIFICATION OF INTRACARDIAC AND AORTIC-PULMONARY SHUNTS. *C. B. Chapman,* J. F. Glover, J. H. Mitchell and W. F. Miller.* Dept. Internal Medicine, University of Texas, Southwestern Medical School, Dallas, Tex.

T-1824 dye curves were recorded oximetrically during cardiac catheterization in forty-seven patients with congenital heart disease, in seventeen normal subjects and in six patients with congestive failure. Appearance (AT), build-up (BT), peak (PT), passage (DUR), and disappearance times (DT) were measured.

With predominantly left-to-right shunts, the ratio DT:AT correctly indicated the shunt in 88 per cent of the cases available. In patients with mixed or predominantly right-to-left shunts the most valid predictive measurement was AT. The ratio BT:AT was no more and possibly less effective than AT. Double peaked curves with early appearance times occurred in six cases, but in two no arterial desaturation occurred. Calculation from double peaked dye curves of the size of the venous-arterial shunt was disappointing. Attempts to correlate BT:AT with per cent arterial saturation and with size of the right-to-left shunt as determined from blood oxygen data failed, but a barely significant correlation developed between AT and per cent arterial saturation. It is concluded that, although the dye curve technic is almost indispensable in differential diagnosis of intracardiac and aortic-pulmonary shunts, its use for quantitation of shunts, and for certain ratios derived from the curves is questionable.

PLASMA I-131 CONCENTRATIONS AFTER ORAL ADMINISTRATION OF I-131 LABELED ALBUMIN. *J. C. Coberly, A. P. Murphy and W. H. Cargill.** V. A. Hospital and Emory University School of Medicine, Atlanta, Ga.

Plasma levels of radioiodine were determined by scintillation counting at varying intervals after oral ingestion of 2 mc./kg. of radioiodinated serum albumin (RISA) in 50 gm. of casein. In ten normal subjects a peak plasma concentration ranging from 6.0 to 8.4 per cent (average 7.5 per cent) of the ingested dose was reached in from forty-five to 120 minutes (average ninety-four minutes). In eight patients with clinically proved pancreatic insufficiency lower peaks (1.1 per cent to 7.6 per cent, average 4.7 per cent) were reached after longer periods of time (150 to 324 minutes, average 215 minutes). In two of these patients the rate of absorption was significantly increased but the peak concentration was not altered by the addition of pancreatin to the test meal. In another patient pancreatin had no effect on the absorption curve. This patient was suspected of having defective absorption rather than lack of proteolytic enzymes on the basis of a positive reaction to the Schilling test (Co^{60} labeled B_{12} absorption), and laparotomy revealed extensive granulomatous lesions, probably sarcoid, of the mesentery.

It is believed that the addition of pancreatin to the test meal will prove helpful in the selection of patients for pancreatin therapy, and in distinguishing diseases which impair absorption from those characterized by deficiency of proteolytic enzymes.

MANGANESE DEPLETION AS AN ETIOLOGICAL FACTOR IN HYDRALAZINE DISEASE. *P. Comens* (introduced by H. A. Schroeder*). Hypertension Division, Dept. Internal Medicine, Washington University School of Medicine, St. Louis, Mo.

The induction of "hydralazine disease" in dogs with lupus erythematosus cells in the blood and pathologic changes in the kidneys consistent with disseminated lupus erythematosus was reported. Hydralazine chelates several trace metals: (1) This drug was administered to ten-day old cockerels, 10 mg. per day. In all perosis developed within six weeks, a disease considered to result from manganese deficiency. Another group was simultaneously fed hydralazine and

manganese citrate, 5 mg. per day, and in all development was normal. (2) Manganese inhibited the *in vitro* formation of the lupus erythematosus cell in human subjects in concentrations of 1×10^{-2} molar; copper, cobalt, zinc and iron caused no inhibition. (3) Rats convulse in about an hour when injected with hydralazine. Manganous glycerophosphate or pantothenic acid injected five to thirty minutes later prevented convulsions. Five other trace metals and pyridoxine had no effect. (4) While in all dogs fed hydralazine alone the lupus-like syndrome developed, no glomerular wire loops appeared in two dogs given parenteral manganous citrate concomitantly. Studies are underway in dogs to ascertain whether or not the lesions of the kidney are reversible. (5) Three patients with hydralazine disease and two with disseminated lupus have apparently improved symptomatically when manganous ion was administered; in the former hydralazine was continued. The evidence suggests that hydralazine may produce "hydralazine disease" by binding manganous ion, possibly blocking dependent enzyme systems.

FACTORS AFFECTING CEREBRAL DAMAGE FOLLOWING CIRCULATORY ARREST. *J. W. Crowell* (introduced by A. C. Guyton*). Dept. Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Miss.

Damage to the central nervous system is quite common in those patients in whom circulatory arrest occurs; indeed, severe damage may result after only four to five minutes of arrest. Prior administration of heparin or of the fibrinolytic activator varidase® has been shown in this laboratory to decrease the degree of cerebral damage. Five out of six dogs pretreated with varidase and subjected to fifteen minutes of circulatory arrest lived, and three of these showed no detectable evidence of cerebral impairment, although some transient effects were noted. Only one out of approximately forty control animals has even lived after this duration of arrest. The above evidence indicates that the cause of the permanent cerebral damage is not lack of oxygen during the period of arrest but is, rather, thrombosis of the smaller vessels. It was also deduced that reducing the cerebral metabolic rate during cerebral ischemia might prevent cerebral damage. Therefore, two dogs were given 20 units/kg. of insulin and during the hypoglycemic period subjected to fifteen minutes of circulatory arrest. Both survived and showed practically no cerebral damage postoperatively.

SERUM PROTEIN-BOUND GLUCOSAMINE AND GALACTOSAMINE. *W. P. Deiss, Jr. and R. F. Willard* (introduced by J. V. Warren*). Dept. Medicine and Biochemistry, Duke University School of Medicine and V. A. Hospital, Durham, N. C.

Elevations of serum mucoprotein and protein-bound carbohydrate have been reported in many apparently diverse clinical conditions, namely, "collagen diseases," acute and chronic inflammatory lesions, those following surgical procedures, and metastatic malignancy. It has been postulated that this increase is related in some way to proliferating connective tissue which is rich in mucoprotein. The possibility that there may be qualitative differences in the serum mucoprotein in these disorders that might give a clue to the nature of the underlying tissue alteration has been investigated. The hexosamines, characteristic constituents of these carbohydrate-containing proteins, were fractionated on ion exchange columns; the glucosamine/galactosamine ratio being taken as a measure of qualitative difference in carbohydrate-bound protein.

In normal whole serum hydrolysates and in Winzler's acid mucoprotein fraction two hexosamines are present: glucosamine (90–95 per cent) and galactosamine (5–10 per cent). The fraction prepared according to Dische by ethanol-potassium hydroxide precipitation, however, yields only glucosamine. Hexosamine was found in all serum protein fractions separated by starch zone electrophoresis with the majority in the alpha globulins. In all the pathologic serums tested (three subjects with rheumatoid arthritis, two with acute rheumatic fever, one with disseminated lupus erythematosus, two with Buerger's disease and two diabetics with Kimmelstiel-Wilson syndrome) the glucosamine/galactosamine ratio resembled very closely that found in normal serum. Thus it appears that there is no qualitative difference in protein-bound hexosamine in the limited series studied.

DEMONSTRATION OF PATHWAYS OF COLLATERAL BLOOD SUPPLY TO THE MIDDLE CEREBRAL ARTERY IN THE MONKEY. *G. S. Dugger, D. P. Jones, T. W. Farmer* and C. W. Fowler.* Divisions Neurosurgery and Neurology, University of North Carolina School of Medicine, Chapel Hill, N. C.

With carotid or middle cerebral artery insufficiency alternative nutrient pathways are known but proof of a collateral supply along the posterior communicating artery is lacking.

With a thermistor applied to the middle cerebral artery the passage of cooled saline through the vessel causes a recordable resistance change. In ten monkeys the circle of Willis and the neck vessels were exposed, a thermistor placed on the middle cerebral artery and 0.25 to 1.0 cc. injections of ice cold saline were made into a neck vessel after occlusion of collateral channels not under study. *External carotid collateral:* The middle cerebral artery was isolated from the internal carotid, the anterior cerebral, the common anterior cerebral, the posterior cerebral and the posterior communicating arteries. External carotid injection did not give a response. *Anterior cerebral collateral:* With the middle cerebral artery supplied only by the anterior part of the circle of Willis, injection of the opposite carotid artery evoked a response. *Posterior communicating collateral:* After occlusion of the anterior part of the circle of Willis, the common anterior cerebral artery and the posterior cerebral artery no response was obtained after subclavian injection (proximal occlusion preventing reflux) but if the carotid artery were then occluded a response was obtained.

INFLUENCE OF ESTERIFICATION ON HYPOCHOLESTEROLEMIC EFFECT OF BETA SITOSTEROL. *C. H. Duncan, M. M. Best* and J. D. Wathen.* Dept. Medicine, University of Louisville School of Medicine, Louisville, Ky.

Administration to humans on unrestricted diet of the plant sterol, beta sitosterol, results in a reduction in serum total cholesterol and other lipids, presumably due to interference with the intestinal absorption of cholesterol. It has been suggested that this interference is due to competition for esterification, a step in the transport mechanism by which cholesterol is absorbed. To test this hypothesis the effect of prior esterification of beta sitosterol has been studied. Rats previously subjected to radiation destruction of the thyroid by I-131, a procedure which augments the elevation of serum and liver cholesterol produced by cholesterol feeding, were used. Groups of four to seven animals were maintained for two weeks on each of the following diets: (1) cholesterol free, (2) 1 per cent cholesterol, (3) 1 per cent cholesterol and 5 per cent beta sitosterol and (4) 1 per cent cholesterol and 7.87 per cent beta sitosterol palmitate. The mean levels of serum total cholesterol (in mg./100 ml.) at the end of the two week period were: 88 ± 16, 119 ± 25, 79 ± 13 and 104 ± 10. The mean levels of liver cholesterol (in mg./100 gm. wet weight) were: 270 ± 28, 1625 ± 296, 281 ± 28 and 1283 ± 533. In the cholesterol fed myxedematous rat beta sitosterol prevent the accumulation of cholesterol in serum and liver. Prior esterification of the sitosterol to a great extent destroys this action.

KINETOCARDIOGRAPHIC AND BALLISTOCARDIOGRAPHIC FINDINGS IN AORTIC INSUFFICIENCY. *E. E. Eddleman, Jr.** V. A. Hospital and Dept. Medicine, Medical College of Alabama, Birmingham, Ala.

Precordial movements (kinetocardiograms) and direct force ballistocardiograms were studied in a group of eighteen patients with "pure" aortic insufficiency. In patients without cardiac enlargement or symptoms it was found that kinetocardiograms and ballistocardiograms were within normal limits. In patients with minimal symptoms there was an exaggerated amplitude of the apex thrust. Moderate symptoms and moderate cardiac enlargement were associated with markedly exaggerated apical impulse which terminated abruptly with the onset of ejection, as determined by the carotid pulse. The patients showing clinical evidence of right and left-sided congestive heart failure also exhibited an exaggerated apex impulse. However, the movements of the lower parasternal region of the chest were similar to those previously noted in patients with right ventricular hypertrophy. In contrast to the altered kinetocardiograms in aortic insufficiency, ballistocardiograms were not consistently changed, and in some patients with marked symptoms ballistocardiograms gave normal results.

Thus there appears to be a correlation between the functional status of the myocardium and the kinetocardiogram. Aortic insufficiency is also apparently associated with specific kinetocardiographic patterns, in contrast to nonspecific ballistocardiograms. In addition, the records were markedly different in pattern from those noted in patients with mitral stenosis or mitral insufficiency.

CEREBRAL BLOOD FLOW AND METABOLISM IN MENTALLY CONFUSED SUBJECTS WITH CONGESTIVE HEART FAILURE. *S. Eisenberg and W. Sensenbach.** Dept. Internal Medicine, Univer-

sity of Texas, Southwestern Medical School and Medical Service of V. A. Hospital, Dallas, Tex.

Thirteen patients with severe congestive heart failure and distinct mental aberrations were studied by the nitrous oxide method of Kety and Schmidt. Comparisons with repeat observations in the lucid state were made in six instances. Results were also compared with the values in eight mentally clear subjects with congestive heart failure of comparable severity.

Results: (1) Cerebral blood flow was consistently decreased in mentally confused subjects with congestive heart failure. The mean cerebral blood flow in the thirteen patients studied was 27 cc./100 gm./minute, as compared to a mean of 42 cc. in eight lucid subjects with congestive heart failure of comparable severity ($p < .05$). (2) Values obtained in six patients with symptoms of mental confusion were compared with observations in the same subjects when lucid; the presence of mental confusion was associated with a marked decrease in cerebral blood flow. (3) The profound decrease in cerebral blood flow in mentally confused subjects was not associated with significant reduction in cerebral oxygen utilization. (4) The suggestion was made that the mental disturbances encountered were related to inadequate cerebral perfusion; this is consistent with other manifestations of inadequate blood flow and cardiac output characteristic of the terminal phase of the congestive process.

THE RELATIONSHIP OF CYTOCHEMICAL CHANGES IN HUMAN LYMPHOID TUMORS OF CHEMOTHERAPEUTIC SPECIFICITY. *L. P. Eliel* and R. P. Heaney.* Cancer Research Section of the Oklahoma Medical Research Foundation and Dept. of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

The nature of chemotherapeutic specificity for neoplastic tissues in man has been explored by means of metabolic balances and cytochemical studies of lymphoid tumors removed for biopsy before and after therapy. It has been possible to demonstrate from balance data and tissue analyses that, whereas cortisone and triiodothyronine induce net catabolism of both neoplastic and normal tissues, 6-mercaptopurine, triethylenemelamine, myleran and demicolcin appear to induce destruction of neoplastic tissues almost exclusively. Analyses of intracellular fractions of leukemic and lymphosarcomatous tissues for N, P, K and the nucleic acids, DNA and RNA, have revealed that specific agents such as 6-mercaptopurine, triethylenemelamine and ionizing radiation appeared to reduce the nuclear contents of DNA, N, P, and K, while nuclear RNA was increased. Cytoplasmic contents of RNA, N, P, and K tended, in general, to rise (with the exception that P and K changes following 6-mercaptopurine have been variable). The non-specific agents appear to have produced slight increases or no change in DNA, and changes in the other analyzed constituents are opposite to those found after administration of specific agents.

The results suggest that the cytologic and chemical sites of action of specific and non-specific agents in the human neoplastic cell differ markedly.

DEMONSTRATION OF A PROTECTIVE SHUNTING MECHANISM IN COLLAPSE. *F. A. Finnerty, Jr.,* J. F. Fazekas* and R. L. Guillaudeu.* Dept. Medicine, Georgetown University School of Medicine and Georgetown University Medical Division, District of Columbia General Hospital, Washington, D. C.

In an attempt to study the relationship between cardiac output and cerebral blood flow in collapse, simultaneous cardiac output (radioiodinated albumin method with multiple arterial sampling) and cerebral blood flow determinations were performed in ten patients. Collapse was induced by lowering the arterial pressure acutely with intravenous hexamethonium and/or by posture. A reduction in mean arterial pressure of 45 per cent resulted in a 47 per cent reduction in cardiac output and a 30 per cent decrease in cerebral blood flow. The level of arterial pressure at onset of collapse varied between 34 to 100 mm. Hg while the level of cerebral blood flow varied between 23 to 40 cc./100 gm. brain/minute. The reduction in arterial pressure resulted in a fall in cerebral vascular resistance in all cases studied, but no consistent changes in peripheral vascular resistance was seen. Control observations revealed that 15 per cent of the cardiac output was diverted to the brain. During collapse, despite a 47 per cent reduction in cardiac output, 20 per cent of the cardiac output was going to the brain. Since the blood volume remained unchanged, these data must be interpreted as demonstrating a protective shunting mechanism during collapse, explaining in part, at least, the not uncom-

mon clinical situation of a conscious patient without obtainable blood pressure.

HEMODYNAMIC EFFECTS OF ANEMIA WITH AND WITHOUT PLASMA VOLUME EXPANSION. *N. O. Fowler, J. A. Ward, R. H. Franch and W. L. Bloom.** Dept. Medicine, Emory University School of Medicine, Atlanta, Ga.

Eleven dogs were bled 1 per cent, 2 per cent and 3 per cent of body weight at half hour intervals. After each bleeding, an equal volume of isoncotic dextran was infused. Ten dogs had similar dextran infusions without bleeding. In the bled dogs, blood volume increase was not significant. In the unbled dogs, the increase (58 to 142 per cent) was significant. Cardiac output increased significantly in both groups (bled, from 175 to 257 cc./kg./minute; unbled, from 163 to 293 cc./kg./minute) and were correlated with change in hematocrit. In the bled dogs, cardiac output rose significantly (183 ± 14, control to 221 ± 14) at a hemoglobin of 7.7 to 10 gm. At a hemoglobin of 4 to 6.2 gm., cardiac output was not significantly different in the two groups. Both groups of dogs showed significant increase in pulmonary arterial pressure and significant decrease in peripheral resistance. Right atrial pressure rose only in the unbled dogs and was not correlated with the increased cardiac output.

The results suggest the possibility that the increase in cardiac output with plasma volume expansion is related to anemia rather than to increase in blood volume.

STUDIES OF MITRAL VALVE FUNCTION EFFECT OF ACUTE HYPERVOLEMIA PREMATURE BEATS AND OTHER ARRHYTHMIAS. *B. Friedman,* W. M. Daily and R. Wilson.* V. A. Hospitals, McKinney, Tex. and Birmingham, Ala., University of Texas, Southwestern Medical College, Dallas, Tex. and Medical College of Alabama, Birmingham, Ala.

A direct method for studying valvular competence has been developed based on changes in impedance in the blood induced by injection of concentrated saline. This method does not require withdrawal of blood samples and tests may be repeated at frequent intervals in the same animal. Mitral regurgitation was thereby detected in dogs in the absence of significant changes in atrial pressure tracings. Mitral insufficiency was observed regularly in association with ventricular flutter and fibrillation, frequently with ventricular premature beats and less often with ventricular tachycardia. Acute hypervolemic states and ectopic rhythms of auricular origin produced mitral insufficiency only under conditions of severe ventricular muscle strain or failure.

RELATIONSHIP OF VENOUS RETURN TO THE DYNAMICS OF CARDIAC DECOMPENSATION. *A. C. Guyton* and A. W. Lindsey.* Dept. Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Miss.

When the heart muscle is weakened the ability of the heart to pump blood is decreased. Yet experiments with dogs in this laboratory have shown that during the early stages of cardiac weakness the cardiac output may not fall appreciably because increased vasomotor tone and increased body fluids increase the tendency for venous blood to return to the heart, thus compensating for the cardiac weakness. However, quantitative experiments have also shown that the compensation which results from increased tendency for venous return reaches a limit. When cardiac weakness goes beyond this limit the cardiac output falls. Also, kidney output falls below normal and will not rise back to normal until the cardiac weakness is corrected or unless a diuretic is administered. As a result, the animal continues indefinitely to collect fluid, which is the state of cardiac decompensation.

CLINICOPHYSIOLOGIC STUDIES IN BURNS. *J. D. Hardy.** Dept. Surgery, University of Tennessee School of Medicine, Memphis, Tenn. and University of Mississippi School of Medicine, Jackson, Miss.

It is necessary to give large amounts of fluid to prevent shock in extensive thermal burns, but such therapy can be excessive. The effects of infused water, salt and colloid solutions upon body fluid kinetics were re-examined.

Body weight changes were followed in fourteen subjects. All gained several kilograms during early fluid therapy, and the gain in those whose burns exceeded 40 per cent ranged from 5 to 10 kg. Cardiac output (measured by blue dye and Fick methods and by ballistocardiographs) tended in eleven patients so studied to be normal or subnormal on admission before therapy was begun, but thereafter cardiac output rose progressively for days, in two patients to almost 15 L./min. On different occasions, oliguria was associated with a low normal or elevated cardiac output. The thiocyanate space (seven patients) increased sharply during early therapy, along with body weight. The "insensible fluid

loss" (6 pints), reflecting losses from wounds, unburned skin and lungs, varied in different subjects and even in the same subject from day to day. One patient "lost" almost 5 L. on each of three consecutive days. Plasma electrolyte studies revealed hyponatremia in the more extensively burned persons. Serious potassium and chloride deviations were rare. Hyperchloremic (142 mEq./L.) hypernatremia (176 mEq./L.) was noted in one subject in whom the urine volume ranged from 1 to 3 L./twenty-four hours; the urine contained virtually no sodium or chlorine.

MECHANISM OF APEX BEAT IN SUBJECTS WITH NORMAL AND ABNORMAL HEARTS. *T. R. Harrison,* E. E. Eddleman, Jr.* and T. J. Reeves.* Dept. Medicine, Medical College of Alabama, Birmingham, Ala.

The apex beat has been studied by palpation and by phonetocardiograms. The normal apex beat occurs about .08 second after the onset of the QRS, and .04 second before the beginning of the carotid upstroke, starts simultaneously with the beginning of the H-I downstroke in the ballistocardiogram, and is accompanied by backward movement in the right parasternal region and in the aortic and pulmonary area. At the same time the left precordial area displays outward movement. The relative importance in the genesis of the normal apex beat of the following factors will be discussed: (1) forward thrust on the apex as the aortic annulus descends, (2) physiologic aneurysmal expansion of the thin-walled apex as the thicker base of the left ventricle contracts, and (3) recoil as the right ventricle ejects.

Patients with left ventricular hypertrophy exhibit a more sustained thrust over a wider area, as compared with the gentle tap of the normal apex beat. Certain subjects with infarction in the region of the apex display a thrust over a still wider area with still greater duration. In these conditions aneurysmal expansion appears to be the main feature in the genesis of the apex beat. Similarly, a few patients with angina pectoris exhibit such an exaggerated apex beat during anginal attacks.

SERUM VASOCONSTRICTOR ACTIVITY AND HEMOSTASIS IN THROMBOCYTOSIS. *R. C. Hartmann.** Dept. Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

In some patients with thrombocytosis the prolonged bleeding time and clinical hemorrhage have been attributed to diminished serum vasoconstrictor activity (serotonin). Since platelets have been considered the source of this substance, a relationship has been suggested between the deficiency of the vasoconstrictor in the platelets on the one hand and the prolonged bleeding time and clinical hemorrhage on the other. Such platelets were used for a transfusion experiment.

The donor patient had myeloid metaplasia, severe menorrhagia and bleeding gums, and a platelet count of two million per cu. mm.; a splenectomy had been previously performed, bleeding time exceeded thirty minutes and serum vasoconstrictor activity was about one-eighth of normal. The recipient patient had aplastic anemia with severe thrombocytopenic purpura and carcinoma of the uterine fundus for which hysterectomy was performed; bleeding time exceeding thirty minutes. Infusion of the platelets during the operation resulted in dramatic cessation of the severe bleeding, appreciable circulation of the platelets for more than four hours and prompt correction of the prolonged bleeding time. This type of experiment provides dramatic evidence that any deficiency of the donor's platelets in vasoconstrictor activity is not the primary or sole cause of the donor's prolonged bleeding time.

EFFECTS OF VARIOUS ANESTHETIC AGENTS UPON BLOOD PRESSURE RESPONSES TO EPINEPHRINE. *J. G. Hilton and R. V. Brown (introduced by A. C. Guyton*).* Dept. Pharmacology, University of Mississippi Medical Center, Jackson, Miss. and University of Tennessee Medical School, Memphis, Tenn.

A correlative study of the effects of *l*-epinephrine upon the blood pressure of dogs anesthesized with various anesthetics has been done. The anesthetic agents employed were barbital sodium, pentobarbital sodium, chloralosane and ether. This study failed to show any single anesthetic as being most depressant or less depressant upon the responses to epinephrine, but showed differences in the effects of the anesthetics varying with the size of the dose of epinephrine. The blood pressure of control subjects was significantly different under the various anesthetics. Chloralosane produced blood pressure in control subjects greater than that obtained under ether or barbital. Pentobarbital produced a blood pressure in control subjects greater than that obtained under barbi-

tal anesthesia. Because of the differences in blood pressures in control subjects, all comparisons of the results of the doses of epinephrine were computed by analysis of covariance. These tests showed that at the two highest doses studied the responses under ether anesthesia were lower than those under any other anesthetic. At the intermediate dosage levels, the responses to epinephrine in animals under chloralosane anesthesia were greater than those obtained under any other anesthesia. At the lowest dosage level no significant differences were noted between the responses of the animals while under the various anesthetics.

RENAL CONCENTRATING DEFECT IN POTASSIUM DEPLETED RATS. *W. Hollander, Jr., R. W. Winters, T. F. Williams, M. Holliday, J. Oliver and L. G. Welt.** Dept. Medicine and Pediatrics, University of North Carolina School of Medicine, Chapel Hill, N. C., Dept. Pediatrics, University of Indiana, Indianapolis, Ind. and the Renal Research Unit, Overlook Hospital, Summit, N. J.

The effect of graded potassium depletion on the ability to concentrate urine was studied in adult male Sprague-Dawley rats. Potassium depletion was produced by feeding an electrolyte-free diet supplemented with $NaHCO_3$. Control groups were protected with supplemental potassium chloride. The renal concentrating mechanism was tested by determining the osmotically effective concentration of total solutes of urine excreted during a twelve-hour period which began several hours after the injection of pitressin in oil. On one occasion water deprivation was substituted for pitressin.

The results indicate that (1) the maximum concentration of urine in control subjects (approximately 2500 milliosmols/L.) was reproducible; (2) potassium depletion was uniformly accompanied by a diminished ability to concentrate urine; (3) this defect was demonstrated early and at a time when muscle potassium was reduced by only 12 per cent; (4) the defect is intensified with progressive potassium depletion, but urine may still be concentrated to within 70 per cent of normal despite depletion of major proportion (30 per cent decrease in muscle potassium); and (5) the defect is better correlated with intensity than with duration of potassium depletion.

CHANGES IN ARTHRITIC SYNOVIAL FLUIDS AS A RESULT OF INTRA-ARTICULAR HORMONAL THERAPY. *H. L. Holley,** *D. Platt, K. L. Yielding and W. Pigman.* Dept. Biochemistry and Medicine, Medical Center, University of Alabama, Birmingham, Ala.

In order to provide more information concerning the changes evoked in synovial fluids as a result of the rheumatoid arthritic processes, synovial fluids were collected from persons at the time of acute involvement of the knee joint and after intra-articular injection of a steroid. Electrophoretic analyses were made on fluids from five patients treated with 25 mg. of hydrocortisone acetate; from one treated with 5 mg. of 9-alpha-fluorohydrocortisone acetate and from one treated with 25 mg. of methyl tert-butyl hydrocortisone acetate. The fluids obtained from thirty-four patients treated with hydrocortisone acetate were analyzed for sodium, potassium and total protein (biuret method).

The arthritic synovial fluids aspirated at the acute stage had relative electrophoretic mobilities not unlike that of blood serum. After therapy, in all instances, the relative mobility of the globulin components tended to approach those for the normal joint fluids. The potassium and protein concentrations showed no appreciable change upon improvement of joint symptoms. Although the sodium concentration varied considerably individually, a marked decreasing trend was apparent.

These results are consistent with the concept expressed by earlier workers that in rheumatoid arthritis the permeability of the joint is increased.

THE INFLUENCE OF CHORIONIC GONADOTROPIN ADMINISTRATION ON SERUM LIPID AND LIPOPROTEIN DISTRIBUTION AND ON URINARY 17-KETOSTEROID EXCRETION. *R. P. Howard** *and R. H. Furman.** Oklahoma Medical Research Institute, and Dept. Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

Androgen administration leads to characteristic changes in serum lipoproteins, notably a reduction in alpha-1 lipoprotein concentration and a lowering of the alpha-1/beta lipoprotein ratio. To further knowledge of the effects of endogenous gonadal hormones on serum lipids and lipoproteins, advantage was taken of an opportunity to study the effects of chorionic gonadotropin administration on seven male subjects. Serum lipids were determined chemically, lipoproteins by ultracentrifugation at 1.21 solvent density.

In two subjects with panhypopituitarism the alpha-1 lipoprotein concentration and alpha-1/beta ratio fell significantly; urinary 17-ketosteroid excretion rose significantly, while beta lipoprotein and cholesterol fell only slightly. In two cryptorchid boys the alpha-1/beta ratio fell, and 17-ketosteroid excretion rose significantly. (In one of these boys urinary gonadotropin [FSH] excretion was abnormally high.) In one adult with Klinefelter's syndrome and in two children, one with retractile testes, the other evidencing delayed somatic growth, changes were not significant, although the alpha-1/beta lipoprotein ratio fell in each instance. The mean fall in the alpha-1/beta lipoprotein ratio of the entire group was highly significant ($P < 0.01$). It was concluded that, when a response to chorionic gonadotropin administration in male subjects is elicited, the changes in serum lipids and lipoproteins are characteristic of androgen administration.

VITAMIN B_{12} ACTIVITY OF NORMAL AND LEUKEMIC SERUMS ASSAYED WITH POTERIOCHROMONAS STIPITATA. *G. W. James, III.** Dept. of Medicine, Medical College of Virginia, Richmond, Va.

Poteriochromonas stipitata, a protozoon, is considered to have a specific growth requirement for vitamin B_{12}, thus differing from Euglena gracilis, the usual protozoal test organism. A technic using P. stipitata has been improved so that the vitamin B_{12} activity of human serum and tissue extracts can be assayed. Normal subjects, those with various hematopoietic disorders, with miscellaneous diseases, and particularly patients with both acute and chronic leukemia have been studied. No previous report of the use of P. stipitata with human material has been made.

Eleven patients with chronic granulocytic leukemia showed the highest vitamin B_{12} activity, as much as thirtyfold above normal levels, which were usually less than 100 $\mu\mu$g./ml. This is less than average normal values of 362 $\mu\mu$g./ml. (100 to 900 $\mu\mu$g./ml.) found with Euglena gracilis method. There is no direct correlation with the white cell count; the vitamin B_{12} activity is variable during the course of the treated disease. In two of twelve patients with acute leukemia the levels were elevated but the remainder were normal or slightly elevated. Patients with various other diseases including hematopoietic disorders had serum vitamin B_{12} activity similar to those in the normal group. Assay of liver, spleen and kidney extracts from seven with acute leukemia showed no demonstrable differences from normal tissue.

EXPERIMENTAL STUDIES OF TEMPORARY CORONARY OCCLUSION. *T. N. P. Johns and B. J. Olson (introduced by R. R. Porter**). National Heart Institute and National Heart Institute and National Microbiological Institute, Bethesda, Md.

The possibility exists of relieving patients with acute coronary occlusion by surgical removal of the arterial obstruction. The success of such a procedure is sharply limited by the time interval between coronary occlusion and development of irreversible destruction of heart muscle. In the experiments reported here temporary coronary occlusion has been studied in rats. In this occlusion in animals of the main left coronary artery a large infarct of the left ventricle and septum is consistently produced with 80 per cent of the animals surviving. Groups of albino rats were subjected to coronary occlusion for varying lengths of time ranging from one to sixty minutes. At the end of the periods of ischemia, the occluding devices were removed and coronary artery flow re-established as evidenced by immediate inspection and subsequent injection studies. Serial electrocardiographic studies were made. The extent of myocardial damage was determined at autopsy by gross and microscopic study. Temporary occlusion for periods up to twenty minutes produced gross myocardial infarcts in less than 10 per cent of animals. Temporary occlusion for sixty minutes was followed by gross infarction in 95 per cent.

These studies indicate that in the normal heart coronary occlusion is followed by gross myocardial infarction unless the arterial obstruction is removed in less than one hour. Beyond this critical period relief of coronary artery obstruction does not prevent subsequent myocardial infarction.

SELECTIVE DEPLETION OF LIVER IRON AFTER ECK'S FISTULA AND VENESECTION IN A PATIENT WITH HEMOCHROMATOSIS. *J. E. Johnson, Jr. and M. Weatherby (introduced by R. Gregory**). University of Texas, Medical Branch, Galveston, Tex.

This report concerns the study of a forty-three year old man with hemochromatosis which was manifested by hepatic cirrhosis, diabetes and skin pigmentation. Diagnosis was made from biopsy specimen of the liver. A classic Eck's

fistula was established for portal hypertension. During eleven months, 15.7 L. of blood were withdrawn by periodic venesection without significant improvement in the disease of the liver or diabetes. Eight months later the patient died of carcinoma of the liver. Serum iron level was elevated during venesection but fell to normal during the terminal stages. At autopsy the organs lacked the bronze color of classic hemochromatosis. Hemosiderin pigment was scant but present in abnormal amount in pancreatic islets and acinar tissue, in myocardial fibers and in adrenal zona glomerulosa. Sections of the liver and kidneys showed no iron pigment.

It is suggested that selective depletion of liver iron occurred because diversion of portal blood through the Eck fistula reduced excessive iron accumulation in the liver, either directly or by rendering more effective some mechanism peculiar to the liver for disposal of stored iron. These observations emphasize that a patient may not be "iron-free" even if the liver is free of pathologic deposits of iron and the serum iron level is normal.

A Study of Intestinal Motility in Patients with Postgastrectomy "Dumping Syndrome." *G. L. Jordan, Jr., R. C. Overton, O. Creech, Jr.* and M. E. DeBakey.** Dept. Surgery, Baylor University College of Medicine, Houston, Tex.

Jejunal motility has been studied in six asymptomatic postgastrectomy patients and twenty patients with postgastrectomy "dumping syndrome" by measuring intraluminal pressure changes, utilizing a Sanborn manometer. After continuous recording for one hour in the fasting state, all subjects were fed a standard hypertonic liquid meal which produced symptoms in patients with the "dumping syndrome," but failed to produce symptoms in the asymptomatic control subjects. Motility was recorded continuously for an additional hour postprandially. Symptomatic patients had a normal fasting motility pattern, but eighteen of the twenty had hypermotility in the postprandial period. The effect of antispasmotic drugs was studied in eighteen of the symptomatic patients. Hexamethonium and banthine® caused a decrease in fasting motility in all patients tested, while pavatrine® and dactil® were less potent agents. The postprandial response was less constant, but partial or complete relief of symptoms was observed in approximately three-fourths of the patients in whom a definite reduction in postprandial motility was recorded. It is concluded that intestinal hypermotility is a common phenomenon in patients with the "dumping syndrome," and may produce gastrointestinal symptoms, but the vasomotor symptoms cannot be explained on this basis.

Study of Cerebral Function and Circulation in Cheyne-Stokes Respiration. *H. R. Karp, H. O. Sieker* and A. Heyman.** Dept. Medicine, Duke University School of Medicine, and V. A. Hospital, Durham, N. C.

The cyclic alterations in blood gases, cerebral arteriovenous oxygen differences (A-V O_2), the electroencephalogram, and consciousness were correlated in Cheyne-Stokes respiration. Repeated studies were made in seven subjects with periodic breathing associated with heart failure or cerebral vascular disease. Arterial pCO_2 was increased during hyperpnea; oxygen saturation and cerebral A-V O_2 were consistently decreased. Arterial pCO_2 was low in apnea while oxygen saturation and cerebral A-V O_2 increased. The mean changes in arterial pCO_2, O_2 saturation and A-V O_2 during the respiratory cycle were 16, 6 and 23 per cent respectively. Fluctuations of consciousness with increased awareness during mid-hyperpnea were noted in patients with heart failure. The electroencephalographic activity of these patients also changed from the high amplitude slow frequency of apnea to low amplitude fast activity. These alterations in awareness and the electroencephalogram were less pronounced in patients with cerebral vascular disease.

These results indicate that the fluctuations in consciousness and alterations of cerebral electrical activity in Cheyne-Stokes respiration are related to changes in blood gas tensions and cerebral circulation. During hyperpnea when blood gas tensions are most severely deranged, cerebral function paradoxically shows the most improvement as manifested by increased awareness, the electroencephalogram pattern of arousal, and an increase in cerebral blood flow.

Interactions between Plasma Proteins and Acid Mucopolysaccharides in Rheumatoid Arthritis. *G. P. Kerby.** Dept. Medicine, Duke University School of Medicine, Durham, N. C.

The interactions *in vitro* between plasma proteins and acid mucopolysaccharides of ground substance have been studied, using plasma from three groups: (1) persons showing no evidence of inflammation, (2) patients with

significant inflammatory but not rheumatoid disease and (3) patients with rheumatoid arthritis. Protein fractions were precipitated at 37°C. and 5°C. from plasma, with and without added chondroitin sulfate at pH 6.0 to 6.4. The protein content of all fractions was determined, and glucuronic acid was measured in those fractions to which chondroitin sulfate had been added. The amount of glucuronic acid closely paralleled in direction of change the protein content of each fraction, suggesting that the added chondroitin sulfate was associated at least in part with the protein precipitated.

Both the subjects in the inflammatory and the rheumatoid groups yielded fractions which were larger than those of the control group. Both also showed a cold precipitable fraction which was equal to or larger than the corresponding 37°C. fraction, unlike the control group. All fractions from plasma plus chondroitin sulfate were significantly larger in all groups than those from plasma alone, except the cold precipitable fractions from subjects in the inflammatory and rheumatoid groups. No significant differences were noted between the data of rheumatoid arthritis and the inflammatory control groups.

COMPARISON OF DIFFERENT THYROID PREPARATIONS BY NITROGEN BALANCE STUDY. *L. H. Kyle,* J. J. Canary and R. J. Meyer.* Dept. Medicine, Georgetown University School of Medicine, Washington, D. C.

As judged by oxygen consumption and certain clinical observations there appears to be substantial variation in rapidity of action and duration of effect among different types of thyroid hormone. This study concerns comparison of triiodothyronine, thyroxin and desiccated thyroid on nitrogen balance in three euthyroid and three myxedematous subjects. In both types continual daily administration of desiccated thyroid caused increased nitrogen excretion within two days and a maximal effect in two weeks. In the euthyroid subject nitrogen equilibrium was regained within four days after cessation of medication. Single doses of triiodothyronine, thyroxin and desiccated thyroid caused a nearly identical pattern of response with regard to rapidity of action and duration of effect. The intensity of the catabolic response was greater in myxedema. In one obese patient large doses of desiccated thyroid caused marked weight loss and increased nitrogen excretion, both of which terminated abruptly upon cessation of treatment. It appears from these studies that the variation in response observed with different thyroid preparations is related to dosage rather than to any specific feature of the individual preparation. Measurement of nitrogen excretion appears valuable for quantitative comparison of the degree of metabolic acceleration induced by different types of thyroid hormone.

THE EFFECT OF A FACTOR ON INTRACELLULAR DIGESTION OF BACTERIA BY HUMAN LEUKOCYTES. *S. P. Martin* and R. Green.* Dept. Medicine, Duke University School of Medicine, Durham, N. C.

The intracellular destruction of bacteria by human leukocytes was studied, and the effect of a dialyzable factor in human serums was measured. Human leukocytes were obtained by dextran sedimentation in a siliconed system. Micrococcus aureus or Staphylococcus marcescens were phagocytized by these cells, and greater than 90 per cent were destroyed within one hour. If cells were washed with saline after phagocytosis had been completed, the bactericidal capacity of the leukocyte dropped to less than 10 per cent. The bactericidal capacity could be restored by addition of human plasma, a dialysate of plasma, or serum. Restoration also occurred with a dialysate of bovine plasma, or of liver, spleen and kidneys of guinea pigs or rats. The active factor in the dialysate was destroyed by heat at 75°C. for thirty minutes or by strong acids. It can be isolated by chromatography. This factor increased the lactic acid production of leukocytes.

Work is in progress on the nature and metabolic activity of the dialyzable factor involved in intracellular destruction of bacteria.

RECURRENT CRISES IN SICKLE CELL ANEMIA RESPONDING TO CHOLECYSTECTOMY: A SYNDROME APPARENTLY BASED ON CHOLECYSTO- AND CHOLEDOCHO- STASIS. *E. E. Muirhead,* E. R. Halden and B. J. Wilson.* Dept. Medicine and Surgery, University of Texas Southwestern Medical School, Dallas, Tex.

Cholecystic disease and choledochal obstruction by stones have been described in hemolytic anemias. The authors wished to consider a syndrome in sickle cell anemia related to the gallbladder but unattended by stones. This disturbance includes mild to severe epigastric pain, at times into the right upper quadrant and infrascapular area. Chills, fever, nausea, vomit-

ing and joint pains may occur. Clinical jaundice has been persistent and prominent. Hepatosplenomegaly has been present. Evidence for hepatocellular injury has usually been absent. Serum bilirubin concentration has varied between 5 and over 50 mg. per 100 cc. Bile in the urine has been present in four of seven patients. Oral and intravenous cholecystograms have been inconsistent.

Cholecystectomy in five patients has been followed by either complete or almost complete disappearance of the clinical jaundice and the syndrome. Thick bile has been present in the gallbladder at times with a putty-like consistency. Subacute and chronic cholecystitis has been present.

Time in months	−36	−24	−18	−3	−1	0†	+12	+28	+36	+48
Serum bilirubin (mg./100 cc.)	60	2.6	4.2	54	28	8.4	2.2	2.2	2.2	2.0

† Cholecystectomy.

It is proposed that the syndrome results mainly from transient biliary obstruction due to thick bile. The gallbladder appears to be the source of this bile. Persistent jaundice and certain forms of recurrent abdominal crises in sickle cell anemia appear due to disturbances in the gall bladder rather than the liver.

CARBON DIOXIDE INDUCED DYSPNEA IN A PATIENT WITH COMPLETE RESPIRATORY PARALYSIS. *J. L. Patterson, Jr.,* F. P. Mullinax, Jr., T. Bain and J. Kreuger*. Dept. Medicine, Medical College of Virginia, Richmond, Va.

Current theories of the pathogenesis of "dyspnea" involve decreased ventilatory reserve to maximum breathing capacity ratio, increased work of breathing, dyssynergia of respiratory muscles, increased tone of intercostal muscles, and increased stimulus of the respiratory center. Most of the postulated factors were absent in the present experiments. The patient, an intelligent twenty year old woman, had complete loss of intercostal and diaphragmatic muscle function following poliomyelitis. In the Drinker respirator, she was given air, then was given 7 per cent CO_2 in air. Symptoms were timed by blink of the eyes. In two experiments at normal tidal and minute volumes, disturbing breathlessness was experienced after one and a half and four and a half minutes of CO_2 inhalation. The sensation was described as "getting real tired inside my chest," "felt like it was not going deep enough and that if I could only take deep breaths it would go away." In another study the patient was hyperventilated to a low alveolar pCO_2 (22 mm. Hg). Fifteen minutes of CO_2 breathing raised the alveolar pCO_2 to that of high normal (44 mm. Hg) but produced no symptoms whatever.

The results are consistent with the theory that the respiratory center itself acts as the sensory receptor for "dyspnea"; these results are incompatible with other current theories.

A MECHANISM FOR INCREASED CREATINE TOLERANCE IN MYXEDEMA. *J. H. Peters.** Dept. Medicine, Emory University and V. A. Hospital, Atlanta, Ga.

Previous reports have demonstrated that creatinuria in hyperthyroidism is accompanied by increased levels in serum. Serum creatine tolerance curves have revealed that the response pattern in thyrotoxicosis is analogous to the hyperglycemia and glycosuria observable in the diabetic following glucose ingestion. The failure of hypothyroid patients to excrete ingested creatine has not been as easily explainable. Serum creatine tolerance curves have displayed a variety of patterns, and their evaluation has been rendered difficult by complications such as circulatory and renal insufficiency. However, in a limited number of instances of untreated hypothyroidism without detectable cardiac or renal failure a definite alteration of the renal 'threshold' for creatine has been demonstrable. In these patients serum levels following ingestion exceeded those seen in normal or hyperthyroid persons. Five of nine persons with depressed thyroid function evidenced by serum precipitable iodine content of 28 per cent or less exhibited this altered threshold. Of the four others one was a fourteen month old patient with creatinism, and two others had azotemia.

These data indicate (1) that the retention of creatine in hypothyroidism is not primarily due to a high rate of tissue deposition, and suggest (2) that it is attributable to increased reabsorption of creatine by the tubules of the kidney.

VALUE AND LIMITATIONS OF COBALT^{60} B_{12} TEST. *C. E. Rath, P. R. McCurdy, B. J. Duffy, Jr. and J. R. Howley (introduced by H. Jeghers*)*. Dept. Medicine, Georgetown University School of Medicine, Washington, D. C.

The diagnosis of pernicious anemia has become increasingly difficult with the advent of widespread use of hematinics containing folic acid. These preparations may correct the

hematologic picture yet allow the combined system disease to progress. The Schilling test if reliable would permit accurate diagnosis of pernicious anemia in patients without anemia.

The Schilling cobalt^{60} B_{12} test, slightly modified, was studied in over fifty patients with pernicious anemia and other diseases. All fourteen cases with established pernicious anemia excreted less than 7 per cent of cobalt^{60} B_{12} in the urine during a twenty-four hour period. Twelve of these excreted less than 5 per cent. All twenty-two patients who did not have pernicious anemia or disease of the kidney excreted over 8.4 per cent and twenty-one of these excreted over 10 per cent. Eight patients with severe disease of the kidney who did not have pernicious anemia excreted less than 5 per cent; seven of these excreted less than 2 per cent. This excretion was not increased by intrinsic factor. Our results suggest that the Schilling test is an accurate test for pernicious anemia provided disease of the kidney and certain technical limitations are considered.

EFFECT OF COLD ON ESOPHAGEAL MOTOR FUNCTION. *J. C. Respess, F. J. Ingelfinger, P. Kramer and T. R. Hendrix (introduced by K. R. Crispell*).* Evans Memorial and Massachusetts Memorial Hospitals, and Dept. Medicine, Boston University School of Medicine, Boston, Mass.

Swallowing a liquid bolus produces a characteristic pressure complex in the esophagus which may be measured by various methods. The present study attempts to show that cooling the esophagus by repeated swallows of a chilled solution produces profound alterations in the normal swallowing complex and in esophageal motility as seen fluoroscopically. The effect of cooling the entire esophagus with repeated swallows of water at 1°C. was studied fifty-one times in thirty normal volunteers. In all the tests the normal swallowing complex was significantly altered. In all but six of the studies, the final positive wave of the complex was completely abolished.

Iced barium was given and observed fluoroscopically and, as the cooling took place, the esophagus dilated, often reaching a diameter of two times that of normal. At that time, no peristalsis was seen, and the final positive wave of the swallowing complex was abolished. The gastroesophageal segment dilated widely and barium flowed into the stomach without benefit of peristalsis. Simultaneous recordings of esophageal temperatures and pressures made while swallowing water at 1°C. showed a loss of the final positive wave below a temperature of 23°C. Temperatures of 10°C. were often recorded. Concomitant fluoroscopic observation also revealed an absence of peristalsis below 23°C. When the cooling effect was compared with the effect of topical cocainization, it was found that cocainization did not produce any effects similar to that of cooling. Cocainization did not enhance the cooling effect.

The effect of cooling was compared with the effect of banthine.® Banthine abolished the final positive wave in all patients; however, it produced less dilatation and, although primary peristalsis could not be seen fluoroscopically, ineffective secondary peristalsis remained. The gastroesophageal segment responded differently because with banthine it remained closed and supported a column of barium even in the upright position. In the cooled esophagus, this segment remained widely dilated and offered no visible resistance to the forward flow of barium.

HEMATOLOGIC RESPONSES IN PERNICIOUS ANEMIA TO OROTIC ACID. *R. W. Rundles* and S. S. Brewer, Jr.* Dept. Medicine, Duke University School of Medicine, Durham, N. C.

Two patients with pernicious anemia in relapse have responded to oral administration of the non-methylated pyrimidine precursor, orotic acid. One patient with postgastrectomy disease, initial red blood count 2,000,000 per cu. mm., was given 3 gm. orotic acid daily. A reticulocyte peak of 30 per cent occurred on the thirteenth day. A satisfactory hematologic remission ensued. A second patient, initial red blood count 1,480,000 per cu. mm., had a reticulocyte peak of 13.2 per cent after being given 3 gm. of orotic acid daily for thirteen days. Both patients, after five and three months of orotic acid therapy respectively, had satisfactory clinical and hematologic remissions. Other routes of administration, dosage schedules, pyrimidine precursors and derivatives, and the like, are being studied.

The effect of orotic acid in pernicious anemia suggests that vitamin B_{12} deficiency in man leads to impaired synthesis of pyrimidines generally rather than to interference with methylation processes in which folic acid is more definitely concerned.

RELATIONSHIP BETWEEN THE INTRAVASCULAR AND THE EXTRAVASCULAR CIRCULATIONS IN

THE HUMAN FOREARM. *H. W. Schnaper, E. D. Freis* and L. S. Lilienfield.* V. A. and Georgetown University Hospitals, Washington, D. C.

Appropriate dosage of a dye (T-1824) relatively impermeable to capillaries, when injected into the brachial artery, provides significant concentrations in the antecubital veins and negligible concentrations in the systemic circulation. If, prior to injection, the dye is mixed with a labelled substance permeable to capillaries but not to tissue cells (thiocyanate) the washout curves of both the intravascular and extracellular substances can be determined. Although the general shape of the washout curves of T-1824 and SCN paralleled each other up to and including the early downslope, approximately 50 per cent of SCN in the capillaries during this period moved out into the interstitial fluids. The later portions of the downslope diverge, SCN being the shallower. Eventually the rate of return of SCN to the vascular compartment equals and then exceeds the rate of loss. Over a wide range of blood flows, thiocyanate mean circulation time was approximately twice that of T-1824 averaging $2.5 \pm .7$ in ten normal subjects and $2.3 \pm .8$ in eight patients with congestive failure. These results indicate that the circulation of an extracellular substance in the forearm bears a constant relationship to the rate of blood flow and that this relationship is maintained in the presence of congestive heart failure.

POLYSACCHARIDE CONSTITUENTS OF HUMAN GASTRIC CONTENT. *P. Schultz, L. Russell, R. Caputto* and S. Wolf.** University of Oklahoma School of Medicine and the Oklahoma Medical Research Foundation, Oklahoma City, Okla.

This study attempts to settle the question of whether or not polysaccharides in the gastric juice exist as a single large molecular component or as parts of a mixture and to determine also whether or not different clinical conditions might be distinguished by concentrations of these polysaccharides. Gastric contents from twenty healthy persons and sixty-eight patients with either gastric or duodenal ulcer, cancer of the stomach or pernicious anemia were analyzed for the following polysaccharide constituents: hexoses, hexosamines, fucose, glucuronic acid and sialic acid. Proteins and pepsin were determined as reference points.

Hexoses, fucose and sialic acid increased significantly ($P < .01$) among patients with cancer and pernicious anemia in comparison to healthy persons. When compared to proteins, however, the increase was specific for pernicious anemia but not for patients with cancer in whom there appeared a general concentration of components with the exception of pepsin and hydrochloride. The molar ratio hexosamine/glucuronic acid (>15) showed that the predominant polysaccharide was of the neutral type while the wide variations in the ratio between the different components of polysaccharides in different persons showed that they occur as a complex mixture rather than as a single entity.

FACTORS INFLUENCING ADAPTATION OF RENAL GLUTAMINASE TO ACID LOADS. *D. W. Seldin* and F. C. Rector.* Dept. Internal Medicine, University of Texas, Southwestern Medical School, Dallas, Tex.

Effects of equivalent loads of strong acid (NH_4Cl) and buffer acid (NaH_2PO_4) were compared in four groups of rats fed a standard electrolyte deficient diet (SEDD) for fourteen days. Group I received SEDD only; group II received SEDD + 3.75 mEq. NH_4Cl + 2 mEq. KCl; group III received SEDD + 3.75 mEq. neutral sodium phosphate buffer and 2 mEq. KCl; group IV received SEDD + 3.75 mEq. NaH_2PO_4 + 2 mEq. KCl. Daily twenty-four hour urine analyses were done for acid excretion and renal glutaminase activity was measured.

RESULTS

Group	pH	Titratable Acid (mEq./day)	NH_3 (mEq./day)	Glutaminase ($\mu M\ NH_3$/100 mg. dry kidney/hr.)
I	6.4 ± 0.15	0.48 ± 0.15	1.9 ± 0.2	788 ± 39
II	6.4 ± 0.1	0.50 ± 0.12	3.80 ± 0.40	1850 ± 100
III	6.5 ± 0.2	1.30 ± 0.30	1.40 ± 0.20	650 ± 44
IV	5.98 ± 0.1	2.46 ± 0.13	2.08 ± 0.34	675 ± 69

Although loads of NH_4Cl sharply augment renal glutaminase activity and ammonia excretion, equivalent amounts of NaH_2PO_4 are virtually without effect.

Activation of renal glutaminase appears to result, not from prerenal effects of acid loads but rather from the properties of the acid anion which reach the tubular urine. Strong acid

anions appear to accelerate H^+ transport in close proximity to the cite of NH_3 production in the distal tubules, thus activating glutaminase, whereas buffer acid anions can accelerate H^+ transport without drastically lowering urine pH and hence need not necessarily induce glutaminase adaptation.

CARDIAC OUTPUT IN VASODEPRESSOR SYNCOPE. *A. M. Weissler, E. H. Estes,* H. D. McIntosh and J. V. Warren.** Dept. Medicine, Duke University School of Medicine, Durham, N. C.

Previous studies on the cardiac output and hemodynamics of vasodepressor syncope have not yielded entirely satisfactory results. The unpredictability of fainting and the time factor in the direct Fick cardiac output method have made observations infrequent and difficult. Circulatory phenomena, including cardiac output by the dye injection technic, have been studied in sixteen normal young men with spontaneous and nitrite induced syncope. Classic vasodepressor fainting was produced. The cardiac output determined at the height of the reaction was usually not markedly different from the control outputs in the same subjects, although in subjects with severe circulatory collapse there was a moderate fall (average 0.9 L. per minute). The data indicate that peripheral vasodilatation is an important factor in producing hypotension. As yet no cause has been determined for the failure of the heart.to respond to this vasodilatation in the usual fashion, that is, an increased cardiac output. It may be that neurogenic cardio-inhibitory reflexes may prevent the heart from correcting hypotension by increased cardiac output. Hyperventilation and marked respiratory variations in arterial pressure were characteristic of vasodepressor syncope.

THE PROPERTY OF HUMAN SERUM ALBUMIN TO CONCEAL VISIBLE EVIDENCE OF BACTERIAL CONTAMINATION. *R. H. Wichelhausen,* H. W. Clark, V. F. Griffing and L. B. Robinson.* Arthritis Research Unit, V. A. Hospital, Dept. Medicine, George Washington University School of Medicine, and Dept. Chemistry, The Catholic University of America, Washington, D. C.

Eight unfavorable reactions and one death were observed following intravenous use of human serum albumin. All reactions were traced to bacterial contamination, although none of the albumin showed any visible evidence of contamination. In all but one instance re-entry of a vial appeared responsible for the contamination.

Experiments showed that heavy bacterial growth may occur in 25 per cent serum albumin without producing visible turbidity or sediment. Studies were undertaken to find an explanation of this phenomenon. Light scattered by bacteria in various media and concentrations of albumin was measured spectrophotometrically. Theoretic calculations of expected turbidity as a function of size and concentration of bacteria in media with different refractive indices and light absorption properties were in good agreement with experimental data. Results indicate that visible turbidity cannot be expected in concentrated albumin until the bacterial population reaches 120,000,000 organisms per milliliter (Staphylococcus albus), whereas 10,000,000 organisms per milliliter produce turbidity in broth. This is due to combined effect of particle size, effective refractive index and strong light absorption by concentrated albumin. Absence of sediment is due to density and viscosity of albumin. Preliminary studies indicate that zinc precipitation of bacteria may detect contamination in albumin without time consuming bacteriologic examination.

Case Reports

Immunologic Agranulocytosis Due to Mercurial Diuretics*

B. J. Koszewski, M.D. *and* T. F. Hubbard, M.D.
Omaha, Nebraska

In the course of treatment of a patient with congestive heart failure, marked leukopenia and neutropenia were observed after each injection of a mercurial diuretic. The reactions resembled an allergic phenomenon and leukoagglutinins were detected in the serum of the patient.

Only three previous case reports of agranulocytosis due to mercurial diuretics have appeared in the American literature.[1–3] The mechanism of the neutropenia has not been clarified, and a detailed account of our findings seems worthy of report.

CASE REPORT

The patient, a fifty-three year old obese white woman, was first seen in May, 1954, because of complaints of dyspnea on exertion and episodes of hyperpnea at rest associated with dizziness and fainting spells. It was believed at that time that her symptoms were due to a chronic anxiety state with hyperventilation. She was next seen in the hospital on July 24, 1954, because of an episode of severe precordial pain and dyspnea of seven hours' duration. On admission she exhibited a sighing type of respiration but was not orthopneic. The blood pressure was 165/100 mm. Hg. The fundi showed grade II chronic hypertensive changes. The chest was clear and there was no distention of neck veins. The heart exhibited a regular rhythm with a rate of 92 and a soft, apical, systolic murmur. There was grade I to II ankle edema. X-rays of the chest showed slight left ventricular enlargement and a small effusion in the right costophrenic angle. Electrocardiogram revealed right bundle branch block. Hemogram showed 4.28 million red blood cells, 13.8 gm. hemoglobin and 8,400 white blood cells, with normal distribution of cells. The platelet count was 280,000; the blood group was A-Rh positive. It was concluded that the patient had mild congestive failure.

On the second hospital day she received 2 cc. of mercuhydrin® intramuscularly and shortly thereafter experienced severe precordial pain, a shaking chill and tachycardia, with a temperature rise to 101.4°F. Two days later she received a second injection of 1 cc. of mercuhydrin and again exhibited high fever, a shaking chill and tachycardia. On this day the white count was found to be 2,400, with only a rare polymorphonuclear leukocyte in the blood smear. Sternal bone marrow showed hyperplasia of intermediate myelocytes with maturation arrest at this stage. There were very few metamyelocytes, a rare stab form and no mature polymorphonuclear leukocytes in the marrow. Red cell regeneration and megakaryocytes appeared normal. The fever continued and penicillin therapy was instituted. The patient complained of a sore mouth, and irregular shallow ulcers appeared on the oral and pharyngeal mucous membranes and tongue. Treatment with cortisone, 300 mg. daily, was started on July 30th. After four days the peripheral blood count returned to normal and the patient became asymptomatic. On August 4th the sternal marrow still showed myeloid hyperplasia but there was an essentially normal proportion of the various myeloid cells. Subsequently the cortisone dose was reduced and on August 10th was discontinued.

To establish the cause of the agranulocytosis, mercuhydrin (2 cc.) was again given intramuscularly on August 16th. One-half hour after injection the patient complained of cold and

* From the Department of Medicine, Creighton University School of Medicine, and Creighton Memorial St. Joseph's Hospital, Omaha, Neb.

experienced a shaking chill. Her face became flushed, the respirations rapid and the pulse weak. Her temperature rose to 102.2°F. and the blood pressure dropped to a low of 60/40 mm. Hg. The white cell count dropped from 7,000 to 2,200 in four hours. (Fig. 1.) This drop was

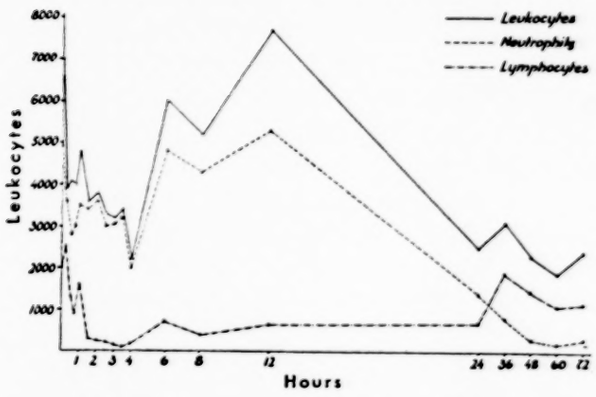


FIG. 1. Changes in the patient's total leukocyte count, neutrophils and lymphocytes (per cu. mm.) after the injection of 2 cc. of mercuhydrin.

followed by a slow rise of the leukocytes to values higher than the original count. A peak of 7,700 leukocytes was reached after twelve hours and this was followed by another decline to a level of 2,500 white blood cells within twenty-four hours. During the first period the number of neutrophils, as well as the number of lymphocytes, was reduced. Of the neutrophils present in the circulating blood, band forms prevailed to an increasing degree as the process progressed. However, the picture of agranulocytosis appeared only in the second period, as the neutrophils disappeared from the peripheral blood and the lymphocytes slowly reached their original values. On August 19th the sternal bone marrow was found to be moderately hypocellular, with the relative proportions of myeloid cells about normal except for a considerable increase in marrow eosinophils. There was a moderate increase in lymphocytes. Red cell regeneration and megakarocytes were normal. With cortisone, 100 mg. per day, the patient's condition again improved. There was no stomatitis at this time. A patch test with mercuhydrin was negative but a skin test with serum drawn from another patient who had just received mercuhydrin was positive. On September 7th, 0.5 cc. of thiomerin was given intramuscularly, following which there was a drop in the white count from 5,300 to 2,300. The curve showed two-phase depression of the neutrophils in the peripheral blood like that noted after exhibition of mercuhydrin. (Fig. 2.) After three days' therapy with cortisone the white blood count rose to 10,000, with a normal differential count. The white count again dropped after cortisone was discontinued

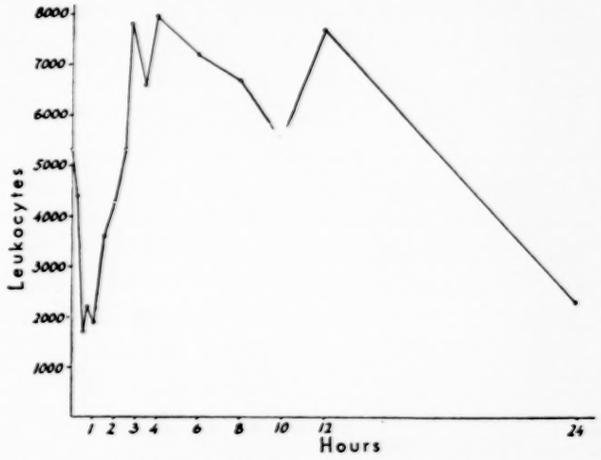


FIG. 2. Changes in the total leukocyte count (per cu. mm.) of the patient following the injection of 0.5 cc. of thiomerin.

but subsequently rose spontaneously to a normal level after six days. The patient showed no subsequent hematologic changes and was discharged from the hospital improved.

EXPERIMENTAL STUDIES

The sudden fall in the white blood count, with severe general symptoms, rise in temperature, shaking chills and shock-like state, following administration of the mercurials suggested a hypersensitivity reaction. The studies reported herein were performed with the intention of elucidating the mechanism of this reaction.

It has been shown that the blood of patients with agranulocytosis may contain a factor which, when infused into the blood of normal recipients, causes a marked drop in the number of circulating neutrophils.[4,8–10] In the present case 300 cc. of blood obtained from our patient on the third day after mercuhydrin administration caused marked leukopenia in a group-compatible recipient. (Fig. 3.) The leukocyte count dropped from 12,100 to 3,900 in the first hour and the subject experienced chills, malaise and a rise in temperature to 101.2°F. The greatest depression was observed in the neutrophils but there was a decrease also in the number of lymphocytes. In the subsequent six hours the leukocyte count returned to the original value

and no leukopenia was observed in the recipient on the following day. Transfusion of the patient's blood to another subject of the same blood group six days after administration of the mercurial and two days before recovery caused minimal changes. The depression of the leukocyte count

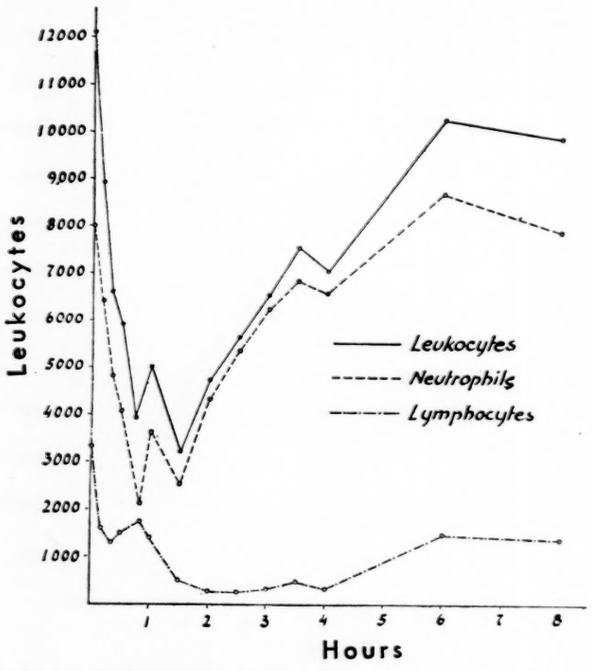


FIG. 3. Changes in the leukocyte count (per cu. mm.) of a normal subject after receiving a transfusion of 300 cc. of the patient's blood drawn three days after the injection of mercuhydrin.

was from 5,400 to 4,100 within one and a half hours. (Fig. 4.) It was followed by an increase in the count to 8,700 with no subsequent change.

This phenomenon has been ascribed to the presence of leukolysins[4–9] or leukoagglutinins[10–12] in the blood of the agranulocytotic subject. To determine the presence of leukoagglutins in the patient's blood, serum specimens were added to suspensions of leukocytes from normal persons of the same blood group. The leukocyte suspension was prepared in silicone-coated tubes by a modification of the method of Finch et al.[31] using dextran for rapid sedimentation of the blood. The serum from the patient was obtained under aseptic conditions and was used immediately for the test: 0.1 cc. of serum was added to 1.0 cc. of leukocyte suspension and, after shaking, was placed in an incubator for one hour at 37°c. The presence of agglutination was determined by microscopic observation at intervals of ten minutes.

Marked agglutination could be observed with the serum specimens drawn two, three and four hours after administration of the mercurial. Control studies with serum of several normal individuals revealed only occasional mild degrees of clumping. With serum drawn six, eight and

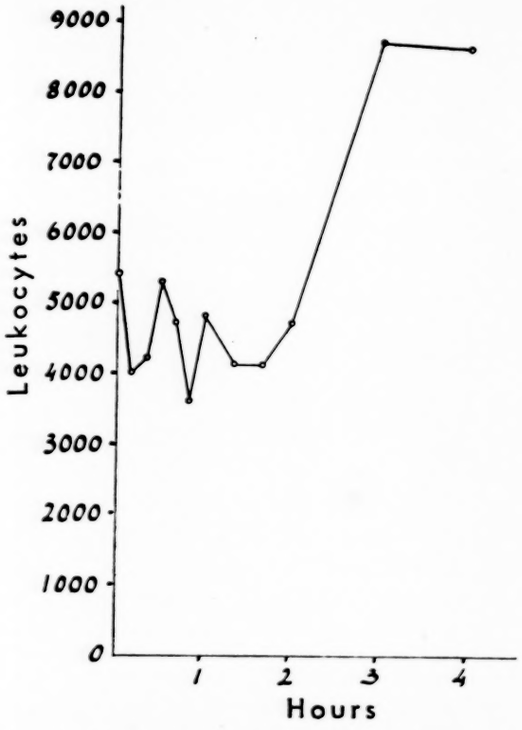


FIG. 4. Changes in the leukocyte count (per cu. mm.) of a normal subject after receiving a transfusion of 300 cc. of the patient's blood drawn six days after the injection of mercuhydrin.

twelve hours after administration of mercuhydrin no significant agglutination beyond that obtained with controls was seen. There was no increase in *in vitro* agglutination in the following days, despite pronounced neutropenia in the blood of the patient. Surprisingly, the suspension of the patient's leukocytes with her own serum did not produce any agglutination, even when mercuhydrin was added in increasing concentrations.

Leukolysis, as determined by serial cell counts at intervals of thirty minutes for four hours, did not occur either with the incubated whole heparinized blood of the patient or with serum-leukocyte suspensions prepared in the manner described.

COMMENT

In spite of the extensive use of the organic mercurials as diuretics, relatively few reports of

adverse effects due to these agents have appeared. Effects associated with excessive activity of the drug include disturbances of fluid and electrolyte metabolism, renal shutdown and sudden death. Probable allergic reactions include chills, fever, vomiting, anaphylactoid reactions, eczema, exfoliative dermatitis and asthma.[13–16] Agranulocytosis due to mercurial diuretics has also been observed,[1–3] but the mechanism of this reaction has not been studied. The clinical pattern of the reaction in our patient suggested hypersensitivity.

Franke,[5] Oliva and Furbetta,[6] Ninni,[7] Wiard and Robbins,[8] and Butzengeiger[9] have been able to demonstrate leukolysins in the peripheral blood of certain patients with granulocytopenia. They postulated that circulating antibodies cause the destruction of cells and neutropenia. Moeschlin and Wagner,[10] stimulated by the work of Ackroyd[20] and Harrington et al.[21] on thrombocytopenic purpura, reported that the blood of a patient with acute amidopyrine agranulocytosis caused transient leukopenia when transfused into healthy volunteers. They also noted that the patient's serum agglutinated normal leukocytes *in vitro* and concluded that this mechanism plays an important role in the pathogenesis of agranulocytosis. Tullis et al.[22] and Dausset et al.[23] were able to show the presence of leukoagglutinins in the serum in many other leukopenic states such as acute aleukemic leukemia, Hodgkin's disease, lymphosarcoma, paroxysmal nocturnal hemoglobinuria and chronic idiopathic pancytopenia, suggesting that immunologic mechanisms play a greater role in these conditions than hitherto suspected.

In our case leukolytic phenomena were not detectable since the serum failed to destroy *in vitro* the leukocytes obtained from the patient or normal subjects. However, the serum caused agglutination of normal leukocytes when tested in the first four hours after the parenteral injection of mercuhydrin. During the following six days the agglutination *in vitro* was not detectable, although transfusion of the patient's blood to a normal individual induced depression of the leukocytes in the recipient. These findings are similar to those in cases of agranulocytosis due to amidopyrine and suggest a similar mechanism.

Moeschlin[24] believes that the leukocytes are clumped by antibodies in the peripheral blood and removed from the circulation by the lungs.[25,26] The behavior of the leukocytes in our case after injection of mercurial (Fig. 1 and 2) would support some such mechanism. The initial depression of the white blood count may be explained by the intense destruction of the agglutinated peripheral leukocytes. With the decrease of the agglutinin activity after four hours, as shown in our case by negative *in vitro* tests, the blood count returned to normal or surpassed the original values, presumably due to stimulation of bone marrow with the release of young stab neutrophils. However, some antibody activity remained in the circulation, as has been shown by our transfusion experiments. It apparently continued to cause the destruction of leukocytes and led to exhaustion of the bone marrow and neutropenia within twenty-four hours. With the disappearance of agglutinin activity in the peripheral blood on the sixth to eighth days, the number of neutrophils progressively increased and recovery was initiated.

Animal experiments with antileukocytic serum also support the theory that the agranulocytosis may be caused by agglutinins. As Metschnikoff,[27] Ledingham and Bedson,[28] Lindstrom,[29] Chen et al.[30] and recently Finch et al.[31] and Zimmerman et al.[32] have shown, the leukocytes can act as a specific antigen. By repeated injection of leukocytes into certain animals an antileukocytic serum may be obtained which causes striking agglutination of leukocytes *in vitro*. A single parenteral injection of antileukocytic serum usually caused transient leukopenia in animals of the same species, but prolonged granulocytopenia has also been observed.[29,31] With repeated subcutaneous injections of serum Moeschlin et al.[33] regularly obtained granulocytopenia in guinea pigs and could observe bone marrow changes characteristic of agranulocytosis with disappearance of mature cells and predominance of young myeloid forms in the marrow.

A relationship between the leukopenia and the leukoagglutinins seems likely but the exact mechanism whereby drug sensitivity causes cell destruction in man remains obscure. It would seem likely that the antibody is constantly present in the blood of the sensitive individual and is in some way activated by the presence of the mercurial compound. However, no agglutination of leukocytes was observed in the peripheral blood after administration of mercurials despite the pronounced fall in the white cell count. Also, no clumping of leukocytes was seen in the cross transfusion experiment although the general reactions were quite severe. The

antibodies from our patient would agglutinate the leukocytes from individuals of a similar blood group *in vitro* but did not clump the patient's own leukocytes. This was also true when the theoretic antigen, mercuhydrin, was added to the system, and similar observations have been made in other cases of immunologic leukopenias.[23] The nature of this resistance of the leukocytes to their own serum is unknown. It is possible that the drugs do not produce antibodies but change the physical properties of the serum and facilitate the agglutination of leukocytes and their destruction in tissues. It would be especially interesting to know the role in this mechanism of the leukotoxins, the presence of which in the serum of human beings has been demonstrated by Doan,[34] Wichels and Lampe,[35] and recently by Tullis.[22]

Allergy to mercurials could be demonstrated in our case by positive skin tests. The response to cortisone was also noteworthy and perhaps also supports the theory of a hypersensitivity mechanism. After three to four days of therapy the leukocytes returned to normal and remained normal so long as the treatment was maintained. The withdrawal of cortisone regularly caused a transient depression of the white blood cells, which required another four days to return to normal. It is our impression that this form of treatment is preferable to the recommendations of Bender et al.[1] who claim good results with BAL.; however, it is likely that most cases of immunologic agranulocytosis which are recognized early will not cause severe bone marrow damage and recovery will occur spontaneously after six to eight days.[17–19] Such patients probably need only antibiotics and general supportive care.

SUMMARY

A case of agranulocytosis due to parenterally administered mercurials is reported. Leukocyte agglutinins could be observed in the serum only in the first four hours after onset of the reaction, although for the next six days the patient's blood retained the capacity for inducing leukopenia when infused into normal recipients. The reactions resembled allergic phenomena. An immunologic mechanism for the agranulocytosis is discussed.

REFERENCES

1. Bender, C. E., Hoxsey, R. J. and de Marsh, Q. B. Neutropenia in a patient treated with a mercurial diuretic and its response to BAL. *Ann. Int. Med.*, 33: 1285, 1950.
2. Silverman, J. J. and Worthen, J. F. Agranulocytosis in a patient treated with mercurial diuretics. *J. A. M. A.*, 148: 200, 1952.
3. Cerf, A. Z. Neutropenia following the injection of mercuhydrin; report of a case. *Stanford M. Bull.*, 11: 154, 1953.
4. Pennati, V. and Testolin, M. Sull agranulocitosi: contributo clinico e spermimentale. *Haematologica*, 13: 259, 1932.
5. Francke, E. Nachweis von Zellgiften im Blut bei Myelophthisen und deren Wirkung auf die Hämatopoese. *Klin. Wchnschr.*, 19: 1053, 1940.
6. Oliva, G. and Furbetta, D. Ancora sull' attivitta leucolitica del plasma nell' agranulocytosi e sulla peculiara "resistenza" delle forme bianche immature. *Haematologica*, 29: 489, 1946.
7. Ninni, M. Contributo allo studio delle leukolisine. *Arch. per le sc. med.*, 86: 444, 1948.
8. Wiard, B. A. and Robbins, S. L. Hypersplenism; a case report with postmortem study. *Blood*, 7: 631, 1952.
9. Butzengeiger, K. H. and Gartz, M. Zur Frage der Nachweisbarkeit eines leukocytenzerstörenden Stoffes im Blute bei der Panmyelophthise. *Klin. Wchnschr.*, 28: 495, 1950.
10. Moeschlin, S. and Wagner, K. Agranulocytosis due to the occurrence of leukocyte agglutinins. *Acta haemat.*, 8: 29, 1952.
11. Dausset, J. and Nenna, A. Présence d'une leucoagglutinine dans trois sérums de malades leucopeniques. *Sang*, 24: 410, 1953.
12. Mavtensson, J. and Vikbladh, T. Idiopathic immuno-neutropenia. Report of a case with a leukocyte agglutinating factor in the serum. *Blood*, 9: 632, 1954.
13. De Graff, A. C. and Nadler, J. E. A review of the toxic manifestations of mercurial diuretics in men. *J. A. M. A.*, 119: 1006, 1942.
14. Gelfand, M. L. Hypersensitivity to mercuhydrin with positive skin test to post-treated mercuhydrin serum. *J. Allergy*, 20: 404, 1949.
15. Ochota, L. Klinischer Beitrag zur Quecksilbervergiftung. Inaug. Diss. Zurich, 1950.
16. Whitman, J. F. and Proudfit, W. F. Hypersensitivity to mercuhydrin. *Circulation*, 6: 245, 1952.
17. Dameshek, W. Leukopenia and Agranulocytosis. New York, 1944. Oxford University Press.
18. Wintrobe, M. M. Clinical Hematology. Philadelphia, 1951. Lea & Febiger.
19. Rohr, K. Das menschliche Knochenmark, 2 ed. Stuttgart, 1949. George Thieme.
20. Ackroyd, J. F. The pathogenesis of thrombocytopenic purpura due to hypersensitivity to sedormid. *Clin. Sc.*, 7: 249, 1949.
21. Harrington, W. J., Minnich, V., Hollingsworth, J. W. and Moore, C. V. Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura. *J. Lab. & Clin. Med.*, 38: 1, 1951.
22. Tullis, J. L., Editor. Blood Cells and Plasma Proteins: Their State in Nature. New York, 1953. Academic Press.
23. Dausset, J., Nenna, A. and Bregy, H. Leukoagglutinins. v. Leukoagglutinins in chronic idio-

pathic or symptomatic pancytopenia and in paroxysmal nocturnal hemoglobinuria. *Blood*, 9: 696, 1954.

24. Moeschlin, S. Immuno-leukopenien und Immuno-agranulozytosen. *Ann. paediat.*, 182: 255, 1954.
25. Bierman, H. R., Byron, R. L., Kelly, K. H. and Petrakis, N. L. The lung removal mechanism for leukocytes. *Blood*, 6: 770, 1951.
26. Weisberger, A. S., Heinle, R. W., Storaasli, J. P. and Hannah, R. Transfusion of leukocytes labeled with radioactive phosphorus. *J. Clin. Investigation*, 29: 336, 1950.
27. Metschnikoff, E. Sur les cytotoxines. *Ann. Inst. Pasteur*, 14: 369, 1900.
28. Ledingham, J. C. G. and Bedson, S. P. Experimental purpura. *Lancet*, 93: 311, 1915.
29. Lindstrom, G. A. An experimental study of myelotoxic sera. Therapeutic attempts in myeloid leukemia. *Acta med. Scandinav.* (suppl. 22), pp. 1–169, 1927.
30. Chen, W. B., Stephens, D. J. and Lawrence, J. S. Antileukocytic serum. *J. Immunol.*, 30: 301, 1936.
31. Finch, S. C., Ross, J. F. and Ebaugh, F. G. Immunologic mechanisms of leukocyte abnormalities. *J. Lab. & Clin. Med.*, 42: 555, 1953.
32. Zimmermann, H. J., Walsh, J. R. and Heller, P. Production of nucleophagocytosis by rabbit antileukocytic serum. *Blood*, 8: 651, 1953.
33. Moeschlin, S., Meyer, H., Israels, L. G. and Tarr-Gloor, E. Experimental agranulocytosis. Its production through leukocyte agglutination by antileukocytic serum. *Acta haemat.*, 11: 73, 1954.
34. Doan, C. A. The recognition of a biologic differentiation in the white blood cells, with especial reference to blood transfusion. *J. A. M. A.*, 86: 1593, 1926.
35. Wichels, P. and Lampe, W. Die gruppenspezifische Differenzierung der Leukocyten. *Klin. Wchnschr.*, 7: 1741, 1928.

Combined Bacillary and Amebic Ulcerative Colitis Associated with Atypical Pneumonitis and Shigella-Positive Sputum*

EDWARD C. RAFFENSPERGER, M.D.

Harrisburg, Pennsylvania

COMBINED infections of the colon by Endamoeba histolytica and shigella must occur in regions where these infections are endemic. However, Elsom, Rogers and Wood found only eight cases of mixed infections in 382 cases of amebic dysentery in an army general hospital in India.[1] It has been stated that bacillary infection of the colon predisposes amebic infection;[2] the incidence of amebic infestations alone in Pennsylvania from 1926 to 1931 was 0.31 per cent.[3] Bockus states that combined infections do occur, although he does not give the incidence.[4] I have been unable to find any reference to pulmonary manifestations of bacillary infections of the bowel, such as were observed in the case herein described.

CASE REPORT

The patient was a fifty-nine year old Negro man, a steelworker who was admitted to the Harrisburg Polyclinic Hospital on November 26, 1952 because of cough, fever and night sweats. For many years he had had a cough productive of white mucus, usually occurring upon arising. A survey chest roentgenogram one year prior to admission apparently gave negative results. Two months immediately prior to admission the cough became more pronounced and was productive of mucopurulent sputum in increasing quantities. This sputum was occasionally stained with blood. The temperature rose daily to 100° to 101°F. and night sweats were prominent. Associated anorexia and weight loss of an unknown amount had occurred. Past medical history revealed frequent attacks of general malaise. The system review gave negative results.

On physical examination, the patient was a well developed and well nourished Negro man with a temperature of 100.2°F., pulse 100, respiration 20 and blood pressure 134/80. He coughed continuously, producing moderate amounts of mucopurulent material. The breath was fetid. Examination of the lungs revealed bronchovesicular breathing over the entire right lung, breath sounds increased over the left lung posteriorly, occasional inspiratory musical rales and crepitant rales over the left lung field anteriorly and posteriorly, and fremitus and breath sounds increased over the right lung but decreased over the left lung. The remainder of a complete physical examination gave normal findings.

The red blood cell count upon admission to the hospital was 3,720,000 with 11.5 gm. of hemoglobin (Haden-Hausser). The white blood cell count was 7,900 with 70 per cent neutrophils, 27 per cent lymphocytes and 2 per cent eosinophils. The sedimentation rate (Westergren) was 30 mm. in the first hour. Urine analyses, fasting blood sugar, blood urea nitrogen and carbon dioxide combining power were within normal limits. PPD No. 1 and PPD No. 2 gave negative results. Four smears and cultures for acid-fast bacilli gave negative results. Sputum culture, reported following the patient's discharge from the hospital, produced a coliform organism identified as anaerogenic paracolon escherichia. X-rays of the chest were obtained on November 28, December 8, December 15 and December 23, 1952. (Fig. 1.)

The patient's course in the hospital was stormy. The temperature ranged between 100° and 102°F. for the first thirteen days but gradually returned to normal. He was treated with oxygen, penicillin, streptomycin, neo-penil® and terramycin.® From the record it would appear that the patient began to improve when he was given terramycin (500 mg. every six hours). The temperature approached normal and the respiratory rate, which had been at 40 per minute, decreased markedly. Terramycin was continued for twenty-one days and the patient was discharged on January 7, 1953, markedly improved.

The patient was admitted to the hospital a second time on June 20, 1953 because of rectal pain, tenesmus and bloody diarrhea which began on May 27, 1953. The onset was sudden and severe. He averaged four to eight watery bowel movements daily, and one week prior to admission began to pass red blood with each bowel movement. At times the bowel movement ap-

* From the Gastrointestinal Department, Harrisburg Polyclinic Hospital, Harrisburg, Pennsylvania.

1A 1B

FIG. 1. A, chest x-ray taken on November 28, 1952 showing pneumonitis involving primarily the left lung; B, chest x-ray taken on December 23, 1952 showing pneumonitis involving both lower lung fields.

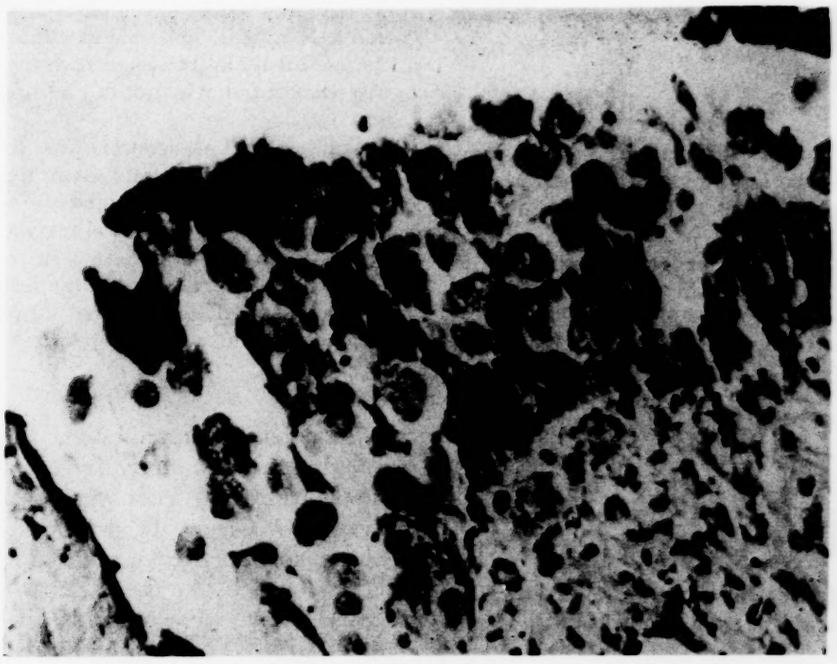


FIG. 2. High power magnification showing cysts of Endamoeba histolytica at the base of an ulcer (rectal biopsy).

peared to consist only of blood. For the five days prior to admission he had bowel movements in small amounts every fifteen to twenty minutes. Tenesmus at the time of and immediately following the bowel movement was severe but abdominal cramps or distention was not marked. Anorexia was prominent, and the patient believed he had lost weight. The cough had improved following his first hospital release and he had been able to work with little respiratory discomfort. Bowel habits had been normal until onset of the present illness.

On physical examination, the patient was a debilitated and dehydrated Negro man in marked distress. Inspiratory rales were noted at both bases and the patient coughed up thick white sputum. On palpation of the rectum the tip of the examining finger encountered a mass which was hard nodular and markedly tender. Bleeding of red blood occurred

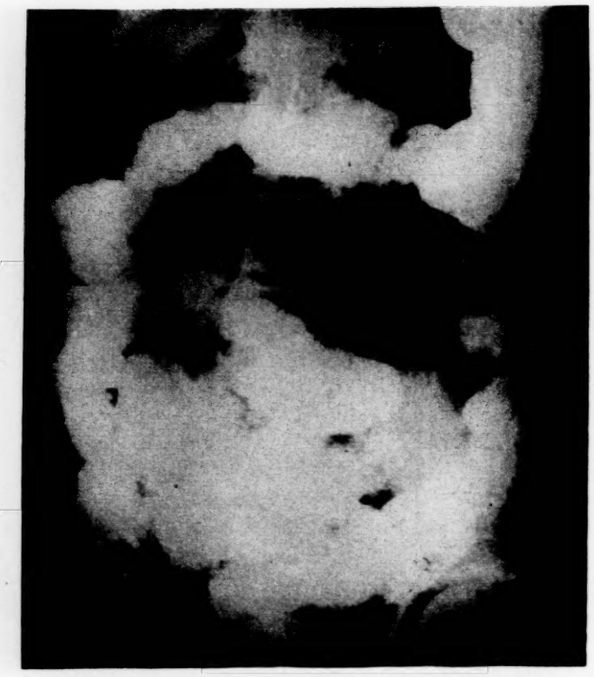


FIG. 3. Barium enema done on June 24, 1953 showing diffuse ulceration of colon.

at the time of the rectal examination. Sigmoidoscopy was attempted but feces and blood obscured the field. The remainder of a complete physical examination gave negative results.

Laboratory examination revealed a red blood cell count of 3,500,000 with 11.5 gm. of hemoglobin (Haden-Hausser). The white blood cell count was 15,350 with 72 per cent neutrophils and 28 per cent lymphocytes. Urine analyses, alkaline phosphatase, blood sugar, blood urea nitrogen, serum bilirubin and bromsulfalein were all within normal limits. Sputum cultures revealed coliform bacilli identified as shigella dysentery Group D (sonnei bacillus). Cultures taken directly from the rectum at the time of sigmoidoscopy revealed shigella dysentery Group D (sonnei bacillus).

On the day following the second hospital admission the patient was again sigmoidoscoped but the degree of involvement suggested by the rectal examination was not visualized. The sigmoidoscope passed into the involved area quite easily. The mucosa was edematous and there were ulcerated areas which had an irregular edge averaging perhaps ½ cm. in diameter. The major involvement seemed to be submucosal, producing prominence of the mucosa. A biopsy was taken from this area and the microscopic section showed cysts of E. histolytica. (Fig. 2.) Roentgenograms of the chest showed clearing of the pneumonitic process previously reported. A barium enema revealed a diffuse ulcerative process involving the entire colon. (Fig. 3.)

From the history and the rectal examination a tentative diagnosis of carcinoma of the rectum had been made in the doctor's office and sulfathalidine therapy, 1 gm. four times daily was instituted upon admission to the hospital as preparation for bowel surgery. With this medication the patient improved markedly, and bowel movements, tenesmus and melena decreased. His appetite returned and the patient was objectively and subjectively better. Repeated attempts were made to obtain culture smears of E. histolytica by taking direct smears from the involved area, but all were unsuccessful. Several more biopsy specimens were obtained but none gave positive results for ameba. However, antiamebic treatment was started on July 1. Emetine, 1 gr. daily, was given intramuscularly for six days. Carbarsone, 3¾ gr. tablets, eight daily, was given for fourteen days. The patient continued to improve clinically and to gain weight. A barium enema performed on July 13, 1953 revealed marked improvement.

The patient was discharged on July 14, 1953, completely asymptomatic. Sigmoidoscopic examination prior to this time revealed minimal inflammatory changes at 6 inches but no area of edema or of ulceration was noted. Some slight subacute inflammatory change involving the lower two inches of the rectum was present but evidence of bleeding or easy friability was noted.

Contact with the patient was lost until February 1954. He had been totally asymptomatic with normal bowel habits and had gained thirty pounds. Barium enema of February 25, 1954 revealed a normal colon except for a constricted area in the mid-descending colon which appeared to be the result of the previous inflammatory disease. Chest x-rays, except for increased trunk markings, were interpreted as normal.

COMMENTS

This patient manifested, at separate times, pneumonitis and ulcerative colitis. Cultures from the sputum and feces were positive for shigella dysentery Group D (sonnei bacillus). Rectal biopsy specimen gave positive results for cysts of E. histolytica. At the time of the pneumonitis bowel habits were normal, yet the sputum culture grew a colon organism. This raises the question as to whether or not this represented a septicemia of colonic origin without colon manifestations. Unfortunately no blood cultures were obtained at this time. The question also arises as to whether or not asymptomatic amebic ulcerations could have been the mode of entry for the bacillary organisms. The marked improvement on sulfathalidine therapy suggests that there was a synergism relating to symptoms between the bacillary and amebic organisms. The mass easily palpable in the rectum but

poorly visualized sigmoidoscopically probably represented an amebic granuloma, as it completely disappeared following therapy.

SUMMARY

A case of combined bacillary and amebic ulcerative colitis, with sputum cultures giving positive results for shigella dysentery Group D (sonnei bacillus) and a preceding pneumonitis with a sputum culture giving positive results of anaerogenic paracolon escherischia, is presented.

REFERENCES

1. Elsom, K. A., Rogers, A. M. and Wood, F. C. Amebiasis in an army general hospital in India. *Gastroenterology*, 8: 135, 1947.
2. VanVoorst Vader, P. J. A. Immunity against bacillary dysentery and infectious enteritis. Connection with flies and amebic dysentery. *Docum. neerl. et indones. morbis trop.*, 8: 83–90, 1951.
3. Rankin, F. W., Bargen, J. A. and Buie, L. A. The Colon, Rectum and Anus, p. 846. Philadelphia, 1932. W. B. Saunders Co.
4. Bockus, H. L. Gastroenterology, vol. 3, p. 661. Philadelphia, 1946. W. B. Saunders Co.

Effect of Intramuscular Heparin on Antibodies in Idiopathic Acquired Hemolytic Anemia*

KARL L. ROTH, M.D. *and* ABRAHAM M. FRUMIN, M.D.
Philadelphia, Pennsylvania

OWREN was the first to note the effects of heparin on the hemolytic process of acquired hemolytic anemia.[1] He restricted his observations to evidence of red cell destruction, no mention being made as to the action of heparin on antibody activity. Since it has been shown that heparin can interact with the adsorbed antibody *in vitro*,[2] it became important to note its effect *in vivo*. The results of these studies in a patient with idiopathic acquired hemolytic anemia are presented and the significance of these observations discussed.

CASE REPORT

R. R., a fifteen year old white girl, was admitted to the Albert Einstein Medical Center, Southern Division, on January 6, 1953 because of weakness, pallor and easy fatiguability of several months duration. Physical examination revealed marked pallor, icterus and moderate splenomegaly. No purpura, glossitis, adenopathy or hepatomegaly was noted. Red blood count was 1.8 million, hemoglobin 6.2 gm. (40 per cent), hematocrit 20, mean corpuscular volume 100, color index 1.0, reticulocytes 33 per cent, platelets 190,000; the white blood count was 7,100 with 5 per cent band forms, 55 per cent segmented forms, 33 per cent lymphocytes, 4 per cent monocytes and 4 nucleated red blood cells per 100 white blood cells. The peripheral blood smear showed many spherocytes and polychromatophilic macrocytes. The sternal marrow aspiration revealed hypercellular marrow with normoblastic hyperplasia. Pertinent laboratory studies showed serum bilirubin to be 3.35 mg. per cent with 2.85 mg. per cent indirect and 0.5 mg. per cent direct; fecal urobilinogen was 664 mg. per day (normal: 40 to 280 mg. per day); plasma hemoglobin was 95 mg. per cent (normal: 0 to 10 mg. per cent); Kolmer test 2+, Kahn test 4+, Eagle test 4+; hypotonic saline fragility was 0.64 per cent to 0.36 per cent (normal: 0.44 per cent to 0.34 per cent). X-rays revealed no abnormalities. A circulating autoantibody was found in the patient's serum and a positive direct Coombs' reaction was obtained. The diagnosis of idiopathic acquired hemolytic anemia was made and treatment with ACTH instituted. A hematologic remission was obtained, although the direct Coombs' reaction still remained positive. The patient was restudied in June 1954 because of recurrence of previous symptoms associated with a fall in the blood count.

METHOD AND RESULTS

Liquaemin,® 5000 units, was injected intramuscularly and duplicate samples (native blood and oxalated blood) withdrawn at one, two and six hour intervals. Oxalated blood was centrifuged and the plasma used for hemoglobin determinations. The red cells were incubated in the serum of the duplicate sample for determination of circulating antibody titers. Standard immunologic technics were employed in all instances. Great care was taken to handle the specimens in similar manner and under constant conditions. The results of two experiments and the values before and after heparin administration are summarized in Table 1.

COMMENTS

The effects of anticoagulants on hemolytic processes have been noted by many observers. Jordan[3] found that the Donath-Landsteiner reaction was negative in the blood samples taken with anticoagulants. Owren[1] described the effect of heparin on the hemolytic process in idiopathic acquired hemolytic anemia without making any reference to antibody activity. Storti[4] confirmed the inhibitory effect of heparin on immune hemolysis in animals sensitized by

* From the Department of Research and Hematology, Southern Division, Albert Einstein Medical Center, Philadelphia, Pennsylvania. This work was supported by Grant #H-1919 from the National Institutes of Health, and by the Joel I. Wagman Foundation, Philadelphia, Pennsylvania.

TABLE I

LABORATORY DATA OBTAINED BEFORE AND AFTER HEPARIN ADMINISTRATION

Date and Dose	Specimen	Titer of Direct Coombs' Test	Saline Agglutinin Titer (37°)*	Serum Bilirubin, Total (mg. %)	Plasma		Reticulocytes (%)	Hemolysis Starts (% saline)
					Hemoglobin (mg. %)	Red Blood Cells (10^6/mm.^{3})		
June 11, heparin, 50 mg., intramuscularly	Before	1:256	1:64	2.85	....	....	....	0.64
	1 hr.	1:256	1:8	....	....	....	....	....
	2 hr.	1:64	1:32	....	....	....	....	....
	6 hr.	1:256	1:64	1.95	....	....	....	0.50
June 18, heparin, 50 mg., intramuscularly	Before	1:64	1:64	....	25.5	2.56	10.2	0.60
	1 hr.	1:32	1:16	....	....	2.51	11.0	....
	2 hr.	1:8	2:32	....	17.6	2.48	12.4	....
	6 hr.	1:16	....	....	6.2	2.97	12.4	0.45

* Cold hemagglutinin, A, B, and heterophile titers were not affected under the conditions indicated. An intravenous injection of 200 mg. protamine sulfate given on a different occasion had no effect whatsoever on the immunologic pattern.

anti-red blood cell serum. Beneficial effects were attributed entirely to the anticomplementary activity of heparin. Storti found no influence on antibody production, such as that suggested by Magerl[5] or Maassen,[6] nor on antibody activity as mentioned by Jorpes.[7] Hummel[8] confirmed the absence of such influence in experimental animals. Crosby[9] showed that minute amounts of heparin will activate the hemolytic mechanism of paroxysmal nocturnal hemoglobinuria *in vitro*, while relatively larger concentrations (that is, 0.00015 per cent or more) will completely inhibit paroxysmal nocturnal hemoglobinuria hemolysis.

The authors' attention was directed primarily to the effects of heparin on antibody activity. The results showed a decrease in the direct Coombs' reaction (bound antibody) and saline agglutinin titer (free antibody). A concomitant decrease occurred in the plasma hemoglobin and serum bilirubin with improvement in the hypotonic saline fragility. It must be remembered, however, that the red cell count and reticulocyte values were virtually unchanged, which may be due to the acute nature of the clinical experiment.

The strong anticomplementary activity of heparin offers a convincing explanation of the inhibition of hemolysis, with prolongation of red blood cell survival.[1] The mechanism of action both *in vitro*[2,10,11] and *in vivo* on autoantibodies remains speculative. We may be dealing with a competition for complement, with resulting inhibition, since heparin and the agglutinins of idiopathic acquired hemolytic anemia are both anticomplementary. Competition for the still mysterious antigen of auto-immunization, or a "simple" charge effect, may also be postulated.

Regardless of the nature of the underlying mechanism, the interaction of heparin with both free and bound antibodies is probably a direct one. The prompt response excludes inhibition of antibody production such as occurs with steroid therapy, since results with the latter are usually not seen before a week or more of such therapy.

Because of this immediate effect on antibodies, heparin should become a useful adjunct in the initial treatment of idiopathic acquired hemolytic anemia. On the other hand its anticomplementary activity may justify its use in any immune hemolytic process, regardless of the presence or absence of agglutinating antibodies.

SUMMARY

The *in vivo* effect of heparin in idiopathic acquired hemolytic anemia was demonstrated. Following a single dose of 5,000 units administered intramuscularly, a fall in the direct Coombs' titer was observed, together with a decrease in circulating auto-antibodies, plasma hemoglobin and serum bilirubin. The hypotonic saline fragility tended to revert towards normal,

although the red blood count and reticulocyte counts were unchanged.

The significance of these observations is discussed and the role of heparin in the initial therapy of the disease postulated.

REFERENCES

1. Owren, P. A. Acquired hemolytic jaundice. *Scandinav. J. Clin. & Lab. Invest.*, 1: 41, 1949.
2. Roth, K. L. Interaction of heparin with auto-agglutinins in idiopathic acquired hemolytic anemia. *Proc. Soc. Exper. Biol. & Med.*, 86: 352, 1954.
3. Jordan. Cited by Storti, E. Atti del Primo Simposio sui Problemi Attinenti alla Coagulazione del Sangue. Genova, 1953.
4. Storti, E. and Vaccari, F. Anticoagulanti ed emolisi. Presented before Congresso Nationale della Soc. Italiana della Transfusione del Sangue. Rome, 1953.
5. Magerl, J. F. Die Bedeutung und Wirkung des Heparins und anderer Blutgerinnungshemmender Stoffe für die Auslösung immunbiologischer Abwehrreaktionen bei bakteriellen Erkrankungen. *Ztschr. f. Immunitätsforsch u. exper. Therap.*, 101: 1, 122, 168, 225, 1942.
6. Maassen, W. Über den Einfluss gerinnungshemmender Wirkstoffe der Leber (Vetren) auf die Agglutininbildung. *Ztschr. f. Hyg. u. Infektionskr.*, 128: 148, 1948.
7. Jorpes, E. Heparin, p. 54. London, 1946. Oxford University Press.
8. Hummel, K., Köhler, R. and Behringer, F. Zur Frage des Einflusses von Heparinpräparaten (Liquemin-Roche und Thrombocid-Benend) auf die Bildung von Antikörpern. *Ztschr. f. klin. Med.*, 148: 597, 1951.
9. Crosby, W. H. and Dameshek, W. Paroxysmal nocturnal hemoglobinuria. The mechanism of hemolysis and its relation to the coagulation mechanism. *Blood*, 5: 822, 1950.
10. Roth, K. L. and Frumin, A. M. Qualitative differences in eluted autoantibodies of acquired hemolytic anemia. *Federation Proc.*, 148: 883, 1955.
11. Roth, K. L. and Frumin, A. M. Studies on the interaction of heparin with the autoantibodies of idiopathic (IHA) and symptomatic (SHA) hemolytic anemias. *Clin. Res. Proc.*, 3: 96, 1955.

AUTHOR INDEX VOLUME XX

Adams, F., 756
Adams, P., 756
Affeldt, J. E., 77
Alcaraz, M., 412
Anderson, W., 860
Arrowsmith, W. R., 941
Asper, S. P., Jr., 732

Badin, J., 500
Bain, T., 954
Bakewell, W., 890
Baldwin, D. S., 217
Barnett, J. C., 153
Baronofsky, I., 756
Baroody, W. G., 314
Barr, P. S., 806
Bashour, F., 361
Bedford, D. R., 301
Beecher, H. K., 107
Bellet, S., 65
Bergy, G. G., 745
Berman, L. B., 941
Berson, S. A., 653
Best, M. M., 946
Bing, R. J., 820
Blain, J. M., 820
Bloom, W. L., 948
Bloomer, W., 157
Blossom, R. A., 77
Boltax, A. J., 418
Bondurant, S. O., 942
Boucek, R. J., 943
Boyce, W. H., 942
Bradley, R. F., 207
Braude, A., 942
Braunwald, E., 869
Brewer, S. S., Jr., 955
Brock, L. L., 745
Brody, E. A., 806
Brown, H., 15
Brown, J. W., 322
Brown, P., 500
Brown, R. V., 949
Browning, J. R., 374
Bruce, R. A., 745
Bruce-Robertson, A., 533
Bryfogle, J. W., 207
Burch, G. E., 943

Canary, J. J., 953
Caputto, R., 956
Cargill, W. H., 943, 944
Casten, G. G., 943
Chapman, C. B., 944
Charles, W. B., 533
Clark, G., 890
Clark, H. W., 957
Clausen, R. E., Jr., 292
Coberly, J. C., 943, 944
Comens, P., 944
Conroy, L., 798
Correa, J. L., 145
Cotton, R. T., 301
Cranny, C., 176
Creech, O., Jr., 952
Crispell, K. R., 23
Crowell, J. W., 945

Daily, W. M., 948
Dam, W., 912
Davolos, D., 760
DeBakey, M. E., 952
Deiss, W. P., Jr., 945
del Pozo, E. C., 412
DeMarsh, Q. B., 798
Dick, F. W., 588
Dobyns, B. M., 684
Dock, W., 853
Dodge, H. T., 834
Donoso, E., 869
Duff, I. F., 510
Duffy, B. J., Jr., 954
Dugger, G. S., 945
Duncan, C. H., 946
Dunlap, W. A., 643
Dunning, M. F., 789

Eckenhoff, J. E., 912
Eddleman, E. E., Jr., 946, 949
Eiseman, B., 890
Eisenberg, S., 189, 946
Eisenmenger, W. J., 879
Eliel, L. P., 947
Epstein, W., 487, 490
Eriksen, N., 564
Estes, E. H., 957

Finby, N., 345
Finch, C. A., 798
Fischel, E. E., 418
Fletcher, A. A., 533
Ford, A. B., 474
Freedman, A. L., 806
Freis, E. D., 956
Farmer, T. W., 945
Favour, C. B., 88
Fazekas, J. F., 947
Finkelstein, D., 65
Finnerty, F. A., Jr., 947
Fowler, C. W., 945
Fowler, N. O., 948
Franch, R. H., 948
French, A. J., 510
Friedman, B., 948
Frumin, A. M., 966
Furman, R. H., 950

Gasster, M., 42
Gaulden, E. C., 624
Gershberg, H., 631
Glover, J. F., 944
Gold, H., 65
Goodale, W. T., 53
Grant, R. P., 334, 834
Green, R., 953
Green, R. S., 760
Griffing, V. F., 957
Grishman, A., 869
Gross, R. E., 53
Guillaudeu, R. L., 947
Guyton, A. C., 948

Halden, E. R., 953
Hall, C. A., 392, 399
Halsted, J. A., 42
Hamlin, J., 23
Handler, F. P., 366
Hannigan, C. A., 793
Hannigan, M. H., 793
Hardy, J. D., 948
Harris, H. W., 308
Harris, S., 114
Harris, T. N., 114
Harrison, H. E., 1
Harrison, J. H., 88
Harrison, T. R., 949
Hartmann, R. C., 949
Heaney, R. P., 947
Heath, D., 322
Heck, F. J., 239
Heller, G., 490
Hellerstein, H. K., 474
Hendrix, T. R., 955
Heyman, A., 952
Hickam, J. B., 942
Hilton, J. G., 949
Hollander, W., Jr., 950
Hollendonner, W. J., 647
Holley, H. L., 100, 950
Holliday, M., 950
Hollifield, G., 23
Hollister, L. E., 643
Houck, G. H., 643
Houghton, J. D., 374
Howard, R. P., 950
Howley, J. R., 954
Hubbard, T. F., 958
Hussar, A. E., 100

Ingelfinger, F. J., 955
Izzo, J. L., 554

Jacobson, A. S., 490
James, G. W., 951
Jeghers, H., 941
Jick, S., 869
Johns, T. N. P., 951
Johnson, J. E., Jr., 951
Jones, D. P., 945
Jordan, G. L., Jr., 952
Juniper, K., Jr., 383

Author Index

Kammerer, W. H., 490
Karp, H. R., 952
Kelly, H. B., 474
Kerby, G. P., 952
King, S. E., 217
Koszewski, B. J., 958
Kramer, P., 955
Kreuger, J., 954
Kuhns, W. J., 251
Kyle, L. H., 953

Lawrence, H. S., 428
Lear, A. A., 896
Lester, C., 145
Lewis, A. J., 163
Lewis, P. M., 42
Lichtman, H. C., 196
Lilienfield, L. S., 956
Lillehei, C. W., 756
Lincoln, A. F., 292
Lindsay, A. E., 15
Lindsey, A. W., 948
Lospalluto, J., 500
Lowell, F. C., 778
Luck, J. M., 317

Mackay, I. R., 564
Mao, F. H., 88
Martin, S. P., 953
Martin, W. J., 239
Matter, M., 798
McCurdy, P. R., 954
McEwen, C., 500
McGavack, T. H., 774
McGeachy, T. E., 157
McIntosh, H. D., 957
Meltzer, J. I., 638
Merendino, K. A., 745
Merrill, A. J., 157
Merten, C. W., 345
Meyer, R. J., 953
Michel, R., 670
Migeon, C. J., 15
Mikkelsen, W. M., 510
Miller, W. F., 944
Minton, R., 145
Mitchell, J. H., 944
Motulsky, A. G., 564
Muirhead, E. E., 953
Mullinax, F. P., Jr., 954
Murphy, A. P., 943, 944
Murtadha, M., 943

Nadas, A. S., 53
Newcomb, T., 798
Nickel, W. F., 879
Noble, N. L., 943
Nugent, C. A., 15

Oliver, J., 950
Olson, B. J., 951
Olson, K. B., 392, 399
Olson, R. E., 159
Ostroff, G., 94
Overton, R. C., 952

Pallotta, A., 941
Pampush, J. J., 745
Parson, W., 23
Pastor, B. H., 647
Patterson, J. L., Jr., 954
Peters, J. H., 954
Pigman, W., 950
Pinney, C. T., 308
Platt, D., 950
Plum, F., 789

Raffensperger, E. C., 964
Ragan, C., 487
Rall, J. E., 719
Ralli, E. P., 631
Rath, C. E., 954
Rawson, R. W., 651
Reckendorf, H. K., 774
Rector, F. C., 956
Reeves, T. J., 949
Respess, J. C., 955
Robinson, L. B., 957
Roth, A., 94
Roth, K. L., 966
Rundles, R. W., 955
Russell, L., 956

Samet, P., 860
Sanford, J. P., 88
Schafer, H., 820
Schier, W. W., 94
Schnaper, H. W., 956
Schreiner, G. E., 941
Schrift, M. H., 94
Schultz, A. L., 30
Schultz, I., 163
Schultz, P., 956
Scott, E. L., 793
Scotti, T. M., 943
Segaloff, A., 941
Seldin, D. W., 956
Sensenbach, W., 946
Shanbrom, E., 145
Shapiro, A., 942
Shapiro, H. D., 196
Sherman, W. B., 603
Shugart, R. T., 314
Siegel, A. L., 820
Sieker, H. O., 952
Siemienski, J., 942
Silberman, H. K., 292

Silverman, B. K., 53
Singer, E., 153
Sinn, C. M., 588
Sjoerdsma, A., 520
Sonenberg, M., 710
Spink, W. W., 176
Steinberg, I., 345
Stetten, D. W., Jr., 817
Stevens, F. A., 185
Stollerman, G. H., 163, 170
Sulkin, N. M., 942
Sussman, O., 153

Taranta, A., 163, 170
Taylor, S., 698
Terepka, A. R., 225

Udenfriend, S., 520

VanArsdel, P. P., Jr., 4
Varco, R. L., 756
Victor, M., 896
Volpe, R., 533
Volwiler, W., 564

Ward, J. A., 948
Warren, J. V., 957
Waterhouse, C., 225
Wathen, J. D., 946
Watson, R. J., 196
Weatherby, M., 951
Weissbach, H., 520
Weissler, A. M., 957
Welt, L. G., 950
Whitaker, W., 322
Wichelhausen, R. H., 957
Willard, R. F., 945
Williams, D. W., 624
Williams, R. H., 4
Williams, T. F., 950
Wilson, B. J., 953
Wilson, R., 948
Winchell, P., 361, 756
Winters, R. W., 950
Wirtschafter, Z. T., 624
Wise, R. I., 176
Wiswell, J. G., 732
Wittenborg, M. H., 53
Wolf, J., 490
Wolf, S., 919, 956
Wood, C., 474
Woolf, W. E., 383

Yielding, K. L., 950

Zevely, H. A., 510
Zieve, L., 30
Ziff, M., 500

SUBJECT INDEX VOLUME XX

(ab.) = Abstracts; (CPC) = Clinico-pathologic Conference; (E.) = Editorial

Abstracts of Southern Society for Clinical Research, tenth annual meeting, Januray 21, 1956, 941
Acid loads, adaptation of renal glutaminase to (ab.), 956
Acromegaly and diabetes (CPC), 133
ACTH and cryoglobulinaemia, 533
Addison's disease and histoplasmosis, 23
Adenomas, adrenal, and Cushing's syndrome, 15
Adrenal
  adenomas, adrenal carcinoma and Cushing's syndrome, 15
  medullary hormones as cause of proteinuria in man, 217
Agranulocytosis and mercurial diuretics, 958
Albumin
  I-131 labeled (ab.), 944
  serum, and bacterial contamination (ab.), 957
Allergy
  and bronchial asthma, 778
  and genesis of antibodies, 114
  and hemolytic streptococcus, 185
  and life stress, 919
  and types and distribution of antibodies, 251
  cold, and cryoproteinemia, 624
  delayed type of inflammatory response in, 428
  diseases, diagnostic methods for, 603
Alseroxylon fraction of Rauwolfia serpentina, 760
Amebiasis, glaucarubin in treatment of, 412
Amebic and bacillary ulcerative colitis, 964
Ammonia metabolism and glutamate therapy in hepatic coma, 890
Analeptics and barbiturate poisoning, 912
Androgen administration and serum lipoproteins (ab.), 950
Anemia
  and monocytic leukemia, 588
  aregenerative, steroid therapy of (ab.), 941
  hemodynamic effects of (ab.), 948
  hemolytic, and heparin, 966
    due to quinidine, 806
  megaloblastic, and absorption of radioactive vitamin B_{12}, 42
  pernicious, and degeneration of spinal cord, 896
    and Shilling cobalt^{60} B_{12} test (ab.), 954
    hematologic responses in (ab.), 955
  sickle cell, responding to cholecystectomy (ab.), 953
    splenomegaly in, 196
Anesthesia, effects on blood pressure (ab.), 949
Aneurysm, syphilitic, of aortic sinuses, 345
Angiocardiography and aneurysms of aortic sinuses, 345
Antibiotic-resistant stains of Micrococcus pyogenes, 176
Antibodies
  genesis of, 114
  types and distribution of, 251
Aortic
  incompetence and ventricular septal defect, 361
  insufficiency, kinetocardiographic and ballistocardiographic findings in (ab.), 946
  pulmonary and intracardiac shunts (ab.), 944
  sinuses, syphilitic aneurysm of, 345
Apex, beat, mechanism of, and the heart (ab.), 949
Argentaffinoma, study of, 520
Arrhythmias and hypervolemia (ab.), 948
Artery, cerebral, blood supply to (ab.), 945
Arthritis
  and changes in synovial fluids (ab.), 950
  rheumatoid, hemagglutination test for, 490
    serologic reactions in (E.), 487
    sheep cell agglutination reaction in, 500
Ascites and portal hypertension in Laennec's cirrhosis, 879
Asthma, bronchial, 778
Atheromatous embolization and renal hypertension, 366
Atrium, flutter of, with 1:1 A-V conduction, 65
A-V arrhythmias, mechanisms of, 334

Bacillary and amebic ulcerative colitis, 964
Bacteria
  and pyelonephritis (ab.), 942
  contamination with, and serum albumin (ab.), 957
  destruction of, by leukocytes (ab.), 953
  differentiation of, in positive urine culture, 88
Ballistocardiographic and kinetocardiographic findings in aortic insufficiency (ab.), 946
Banthine, effect of, on esophageal motor function (ab.), 955
Barbiturate poisoning
  and analeptics, 912
  and hemodialysis (ab.), 941
Beta sitosterol, hypocholesterolemic effect of (ab.), 946
Bicuspid pulmonary valve, isolated congenital, 474
Bile, microspheroliths in, 383
Biliary tract studies, 383
Biology, study of chemical processes in (E.), 817
Blood
  ammonia determinations and hepatic coma, 890
  determinations by counting I-131 and Cr-51 (ab.), 943
  flow, relationship of extracellular substance to (ab.), 955
  gas tensions and Cheyne-Stokes respiration (ab.), 952
  non-protein nitrogen and postnephrectomy renal failure, 157
  plasma, antibodies of, 114
  pressure, effects of anesthesia on (ab.), 949
  supply to cerebral artery (ab.), 945
  volume in Laennec's cirrhosis of liver, 189
Brock type valvulotomy and pulmonary valvular stenosis, 756
Bromide intoxication and mercurial diuretics, 100

Bronchial asthma, 778
Burns, studies in (ab.), 948

Calcium metabolism (E.), 1
Calculi, urinary, matrix of (ab.), 942
Cancer, forced feeding of patients with, 225
Carbohydrate, protein-bound, elevations of (ab.), 945
Carbon dioxide induced dyspnea (ab.), 954
Carcinoid, malignant, 520
Carcinoma, adrenal, and Cushing's syndrome, 15
Cardiac
  and aortic-pulmonary shunts (ab.), 944
  decompensation and venous return (ab.), 948
  emergency and atrial flutter, 65
  failure, molecular events in (E.), 159
  output and anemia (ab.), 948
    and cerebral blood flow during collapse (ab.), 947
    and peripheral gangrene, 301
    in vasodepressor syncope (ab.), 957
    studies in burns (ab.), 948
  symptoms, kinetocardiograms and ballistocardiograms (ab.), 946
Cellular
  destruction of bacteria by leukocytes (ab.), 953
  sources of antibodies, 114
Central nervous system
  infectious mononucleosis of, 643
  lymphosarcomatosis of, 292
Cerebral
  blood flow and cardiac output during collapse (ab.), 947
  damage following circulatory arrest (ab.), 945
  function in Cheyne-Stokes respiration (ab.), 952
  metabolism and congestive heart failure (ab.), 946
Cheyne-Stokes respiration, cerebral function and circulation in (ab.), 952
Cholecystectomy and sickle cell anemia (ab.), 953
Choledochal obstruction and sickle cell anemia (ab.), 953
Cholesterol, serum, following radioactive iodine therapy, 30
Chorea, Sydenham's, and group A streptococci, 170
Chorionic gonadotropin administration (ab.), 950
Circulation
  and Cheyne-Stokes respiration (ab.), 952
  and pulmonary vascular engorgement (ab.), 942
Circulatory arrest and cerebral damage (ab.), 945
Cirrhosis and blood ammonia determinations, 890
Citrate metabolism (E.), 1
Clinic on psychosomatic problems (Massachusetts Gen. Hosp.)
  brief psychotherapy of patient with headache and endometriosis, 286
Clinico-pathologic conferences (Washington Univ.)
  acromegaly, diabetes, hypermetabolism, proteinuria and heart failure, 133
  arthritis, polymyositis and polyneuritis, 462
  central nervous system disease characterized by low spinal fluid sugar, 275
  hypertension, proteinuria and edema, 929
  recurrent burning retrosternal pain, 612
Cold, effect of, on esophageal motor function (ab.), 955
Colitis, ulcerative, with pneumonitis and shigella-positive sputum, 964
Collapse, shunting mechanism in (ab.), 947
Coma, hepatic, ammonia metabolism and glutamate therapy in, 890
Combined staff clinic (Columbia Univ.)
  disorders of renal tubular function, 448
Coronary
  artery disease in diabetic patients, 207
  occlusion, temporary (ab.), 951
Cortisone
  and cryoglobulinaemia, 533
  and cryoproteinemia, 624
  and hyperinsulinism, 631
  and peripheral macrocytosis (ab.), 941
  therapy and Hamman-Rich syndrome, 308
Cr-51 and blood determinations (ab.), 943
Creatine tolerance in myxedema (ab.), 954
Cryoglobulinemia, 533
  and macroglobulinemia, 564
Cryoproteinemia and cold allergy, 624
Cushing's syndrome, diagnosis of, 15
Cytochemical changes in lymphoid tumors (ab.), 947
Cytopenia and monocytic leukemia, 588

Desiccated thyroid and myxedema, 774
Dextrocardia and dextroposition of heart, 647
Diabetes
  and insulin-zinc suspensions, 554
  and myocardial infarction, 207
Dialysis and intracellular destruction of bacteria (ab.), 953
Diets and diagnosis of allergic diseases, 603
Digitalis in atrial flutter, 65
Disorganization, levels of (E.), 817
Diuretics, mercurial
  and bromide intoxication, 100
  and agranulocytosis, 958
Dumping syndrome and intestinal motility (ab.), 952
Dyspnea, carbon dioxide induced (ab.), 954

Ebstein's disease, 322
Eck's fistula and liver iron depletion (ab.), 951
Electrocardiography and left bundle branch block, 834
Embolization, atheromatous, and renal hypertension, 366
Emotional reactions and disease, 286
Endometriosis, psychotherapy of patient with, 286
Enemas, potassium depletion by, 789
Epinephrine, blood pressure responses to (ab.), 949
Erythrocyte sedimentation rate in myocardial infarction, 418
Esophagus, motor function of (ab.), 955
Esterification, influence on hypocholesterolemia (ab.), 946

Fanconi syndrome and renal tubular acidosis, 448

Galactosamine and glucosamine (ab.), 945
Gallbladder and sickle cell anemia (ab.), 953

Gallstones, analysis of, 383
Gamma globulin test and rheumatoid arthritis, 490
Gangrene, peripheral, complicating myocardial infarction, 301
Gastrectomy, intestinal motility after (ab.), 952
Gastric content, polysaccharide constituents of (ab.), 956
Gastrointestinal fluid loss and potassium depletion, 789
Glaucarubin in treatment of amebiasis, 412
Glucosamine and galactosamine (ab.), 945
Glutamate therapy and ammonia metabolism in hepatic coma, 890
Glutaminase, renal, adaptation to acid loads (ab.), 956
Glycosuria, renal, 448
Goiter, nodular, 698
Gonadotropin, chorionic, administration (ab.), 950
Graves' disease, 684

Hamman-Rich syndrome, 308
Headache and endometriosis, psychotherapy of a patient with, 286
Heart
  and mechanism of apex beat (ab.), 949
  block, congenital, 869
  dextroposition of, simulating dextrocardia, 647
  disease and Cheyne-Stokes respiration (ab.), 952
  failure and cerebral metabolism (ab.), 946
    and myocardial metabolism, 820
    congestive, and lungs (ab.), 942
  muscle, destruction of, and coronary occlusion (ab.), 951
  venous blood to (ab.), 948
Hemagglutination test for rheumatoid arthritis, 490
Hematologic responses in pernicious anemia (ab.), 955
Hemochromatosis and liver iron depletion (ab.), 951
Hemodialysis and barbiturate poisoning (ab.), 941
Hemodynamic effects of anemia (ab.), 948
Hemolytic
  anemia and heparin, 966
    due to quinidine, 806
  streptococcus and allergy, 185
Hemorrhagic diathesis of prothrombin complex, 798
Hemosiderosis, idiopathic pulmonary, 374
Hemostasis in thrombocytosis (ab.), 949
Heparin and hemolytic anemia, 966
Hepatic coma, ammonia metabolism and glutamate therapy in, 890
Hexamethonium and vasomotor state (ab.), 943
Hexosamines (ab.), 945
Histoplasmosis and Addison's disease, 23
Hodgkin's disease
  and immunity, 94
  and lymphosarcoma, 392, 399
Hormone
  adrenal medullary, as cause of proteinuria in man, 217
  therapy and arthritis (ab.), 950
  thyroid, 670
Hydralazine disease, manganese depletion in (ab.), 944
17-Hydroxycorticosteroid determinations in Cushing's syndrome, 15
Hyperinsulinism and cortisone, 631
Hypertension
  and loud presystolic sounds, 853
  and Rauwolfia serpentina, 760
  in hepatic venous system, 879
  renal, and atheromatous embolization, 366
Hyperthyroidism and radioactive iodine, 30
Hyperventilation and vasodepressor syncope (ab.), 957
Hypervolemia and mitral valve function (ab.), 948
Hypocholesterolemia, effect on beta sitosterol (ab.), 946
Hypoglycemia and vasomotor lability, 631
Hypotension
  and peripheral gangrene, 301
  and peripheral vasodilatation (ab.), 957
Hypothyroidism
  and retention of creatine (ab.), 954
  and triiodothyronine, 774

I-131
  and blood determinations (ab.), 943
  concentrations after administration of I-131 labeled albumin (ab.), 944
Icterus, familial non-hemolytic, 314
Immunity and Hodgkin's disease, 94
Inflammation, serologic tests for, and myocardial infarction, 418
Insulin-zinc suspensions, 554
Intestinal
  lesions of, and megaloblastic anemia, 42
  motility in postgastrectomy patients (ab.), 952
Iodine
  metabolism, pathways of, 653
  radioactive, and hyperthyroidism, 30
    and thyroid disease, 719
Iron, liver, depletion after Eck's fistula and venesection (ab.), 951
Ischemia, renal, and proteinuria in man, 217

Jaundice of obscure pathogenesis, 314
Jejunal motility in postgastrectomy patients (ab.), 952
Joint diseases, histologic study in, 510
Jugular veins, presystolic sounds over, 853

Ketosteroid excretion and gonadotropin administration (ab.), 950
Kidney
  and potassium depletion (ab.), 950
  scleroderma of, 793

Laennec's cirrhosis
  of liver, blood volume in, 189
  portal hypertension and ascites in, 879
Leishmaniasis, mucocutaneous, visceral manifestations of, 145
Lente insulin and NPH insulin, 554
Leukemia, monocytic, 588
Leukemic serums and vitamin B_{12} activity (ab.), 951

Subject Index

Leukocytes, destruction of bacteria by (ab.), 953
Life stress and allergy, 919
Lipid and lipoprotein distribution and gonadotropin administration (ab.), 950
Liver
  iron depletion after Eck's fistula and venesection (ab.), 951
  Laennecs' cirrhosis of, and blood volume determinations, 189
Lung
  and vascular engorgement (ab.), 942
  biopsy and Hamman-Rich syndrome, 308
Lupus erythematosus and manganese depletion (ab.), 944
Lymphocytes, atypical, and infectious mononucleosis, 643
Lymphomas, malignant, 392, 399
Lymphosarcomatosis of central nervous system, 292

Macrocytosis, peripheral, and cortisone (ab.), 941
Macroglobulinemia and cryoglobulinemia, 564
Malignant
  carcinoid, 520
  lymphomas, 392, 399
  nephrosclerosis (CPC), 929
Manganese depletion in hydralazine disease (ab.), 944
Mediastinum, pendular motion of, 860
Megaloblastic anemia and absorption of radioactive vitamin B_{12}, 42
Mental confusion and cerebral metabolism (ab.), 946
Mercurial diuretics and bromide intoxication, 100
Metabolism
  ammonia, and glutamate therapy in hepatic coma, 890
  and thyroid hormones (ab.), 953
  cerebral, and circulatory arrest (ab.), 945
  citrate and calcium, interrelation of (E.), 1
  during forced feeding of patients with cancer, 225
  following radioactive iodine therapy, 30
  myocardial, in congestive failure, 820
  porphyrin, 239
Micrococcus pyogenes, antibiotic-resistant strains of, epidemiologic studies on, 176
Microspheroliths in bile, 383
Mitral
  valve function and hypervolemia (ab.), 948
  valvulotomy, functional evaluation of, 745
Molecular events in cardiac failure (E.), 159
Mononucleosis, infectious, of central nervous system, 643
Mucocutaneous leishmaniasis, visceral manifestations of, 145
Mucopolysaccharides and plasma proteins in rheumatoid arthritis (ab.), 952
Mucoprotein-mucopolysaccharide matrix of urinary calculi (ab.), 942
Myocardial
  infarction and coronary occlusion (ab.), 951
    and diabetes, 207
    and peripheral gangrene, 301
  metabolism in congestive failure, 820
  rupture following myocardial infarction (CPC), 612
Myxedema
  comparative therapy for, 774
  creatine tolerance in (ab.), 954
  physiology and treatment of, 732

Neoplastic cells, chemotherapeutic specificity for (ab.), 947
Nephrectomy, renal failure after, 157
Neurologic component of degeneration of spinal cord, 896
Nitrogen
  balance study and thyroid preparations (ab.), 953
  mustard and malignant lymphomas, 392, 399

Orotic acid and pernicious anemia (ab.), 955
Oximetric dye in identification of intracardiac and aortic-pulmonary shunts (ab.), 944

Pain, significance of, 107
Pancreatin and I-131 concentrations (ab.), 944
Patent ductus arteriosus and ventricular septal defect with aortic incompetence, 361
Pericardial effusion in scleroderma, 638
Peripheral gangrene complicating myocardial infarction, 301
Physiologic studies in burns (ab.), 948
Pinealoma with widespread metastases to meninges and low cerebral spinal fluid sugar (CPC), 275
Plasma
  electrolyte studies in burns (ab.), 948
  gamma globulins, antibodies of, 114
  17-hydroxycorticosteroid determinations in Cushing's syndrome, 15
  proteins and mucopolysaccharides in rheumatoid arthritis (ab.), 952
  turnover of (E.), 317
  volume expansion and anemia (ab.), 948
Pneumonitis and shigella-positive sputum with colitis, 964
Poliomyelitis, respirator deaths in, 77
Polyarteritis and rheumatoid arthritis (CPC), 462
Polyneuritis, infectious, and lymphosarcomatosis, 292
Polysaccharide constituents of gastric content (ab.), 956
Porphyrins and porphyria, 239
Portal hypertension and ascites in Laennec's cirrhosis, 879
Potassium depletion
  by enemas, 789
  renal concentrating defect in (ab.), 950
Presystolic sounds and high venous pressure, 853
Protein
  bound glucosamine and galactosamine (ab.), 945
  C-reactive, in myocardial infarction, 418
  formation and cryo- and macroglobulinemia, 564
  plasma, turnover of (E.), 317
  serum, electrophoretic analysis of, 624
Proteinuria and renal ischemia, 217
Prothrombin complex, hemorrhagic diathesis of, 798
Psittacosis, human and bird transmitted, 153

Subject Index

Psychologic factors and allergy, 919
Psychotherapy of patient with headache and endometriosis, 286
Pulmonary
  hemosiderosis, idiopathic, 374
  insufficiency, 474
  stenosis with intact ventricular septum, 53
  valve, isolated congenital bicuspid, 474
  valvular stenosis and Brock type valvulotomy, 756
Pyelonephritis, hematogenous, relationship of bacterial species to (ab.), 942

QRS complex prolongation, 834
Quinidine, hemolytic anemia due to, 806

Radioactive
  chromium-tagged red cells and Laennec's cirrhosis, 189
  iodine and hyperthyroidism, 30
    and thyroid disease, 719
  vitamin B_{12}, absorption of, in megaloblastic anemia, 42
Radioiodine, plasma levels of (ab.), 944
Rauwolfia serpentina and hypertension, 760
Relaxin, effects of, in scleroderma (ab.), 943
Renal
  concentrating defect in potassium depletion (ab.), 950
  failure after nephrectomy, 157
  glutaminase, adaptation to acid loads (ab.), 956
  hypertension and atheromatous embolization, 366
  ischemia and proteinuria in man, 217
  tubular function, disorders of, 448
Respirator deaths in poliomyelitis, 77
Respiratory
    paralysis and carbon dioxide induced dyspnea (ab.), 954
  variations and vasodepressor syncope (ab.), 957
Rheumatic fever
  and group A streptococci, 163
  and Sydenham's chorea, 170
  A-V arrhythmias in, 334
Rheumatoid arthritis
  hemagglutination test for, 490
  plasma proteins and mucopolysaccharides in (ab.), 952
  serologic reactions in (E.), 487
  sheep cell agglutination reaction in, 500
Roentgenotherapy and malignant lymphomas, 392, 399

Scleroderma
  and relaxin (ab.), 943
  of kidneys, 793
  pericardial effusion in, 638
Seminar on allergy
  bronchial asthma, 778
  delayed type of allergic inflammatory response, 428
  diagnostic methods for allergic diseases, 603
  genesis of antibodies, 114
  life stress and allergy, 919
  types and distribution of antibodies, 251
Sensation, response and reaction to, 107
Serologic
  reactions in rheumatoid arthritis (E.), 487
  tests for inflammation, 418
Serotonin
  and malignant carcinoid, 520
  and thrombocytosis (ab.), 949
Serum
  albumin and bacterial contamination (ab.), 957
  cholesterol and beta sitosterol (ab.), 946
    following radioactive iodine therapy, 30
  complement in myocardial infarction, 418
  globulin in sheep cell agglutination reaction in rheumatoid arthritis, 500
  lipid and lipoprotein distribution and gonadotropin administration (ab.), 950
  mucoprotein, elevations of (ab.), 945
  vasoconstrictor activity and thrombocytosis (ab.), 949
  vitamin B_{12} and degeneration of spinal cord, 896
Sheep
  cell agglutination reaction in rheumatoid arthritis, 500
  erythrocyte agglutination test and rheumatoid arthritis, 490
Shigella-positive sputum and pneumonitis with colitis, 964
Shilling cobalt^{60} B_{12} test and pernicious anemia (ab.), 954
Shunting mechanism during collapse (ab.), 947
Sickle cell anemia, splenomegaly in, 196
Simmonds' disease, 4
Sitosterol and accumulation of cholesterol (ab.), 946
Skin tests and diagnosis of allergic diseases, 603
Spinal cord, degeneration of, 896
Splenomegaly in sickle cell anemia, 196
Staphylococci, antibiotic-resistant strains of, 176
Stenosis
  pulmonary valvular, and Brock type valvulotomy, 756
    with intact ventricular septum, 53
Steroid therapy of aregenerative anemia (ab.), 941
Streptococcus
  group A, and rheumatic fever, 163
    and Sydenham's chorea, 170
  hemolytic, and allergy, 185
Stress and allergy, 919
Sydenham's chorea and group A streptococci, 170
Symposium on pathologic physiology of thyroid diseases
  foreword, 651
  pathways of iodine metabolism, 653
  physiologic concepts in diagnosis and treatment of Graves' disease, 684
  physiologic concepts in genesis and management of thyroid tumors, 710
  physiologic considerations in genesis and management of nodular goiter, 698
  physiology and treatment of myxedema, 732
  recent progress in physiology and biochemistry of thyroid hormones, 670
  role of radioactive iodine in diagnosis of thyroid disease, 719
Synovial fluids, changes in, in arthritis (ab.), 950
Synovium of knee joint, punch biopsy of, 510
Syphilitic aneurysm of aortic sinuses, 345

Thiocyanate space in burns (ab.), 948
Thrombocytopenic purpura and quinidine, 806
Thrombocytosis, serum vasoconstrictor activity and hemostasis in (ab.), 949
Thyroid
  deficiency and Simmonds' disease, 4
  desiccated, and myxedema, 774
  disease and radioactive iodine, 719
    foreword to symposium on, 651
  hormones, 670
  I-131 uptake following radioactive iodine therapy, 30
  preparations and nitrogen balance study (ab.), 953
  tumors, 710
L-Thyroxine and myxedema, 774
Triiodothyronine and hypothyroidism, 774
D, L-Triiodothyronine and myxedema, 774
Tumors
  lymphoid, cytochemical changes in (ab.), 947
  thyroid, 710

Ulcerative colitis, amebic, with pneumonitis and shigella-positive sputum, 964
Urinary
  17-hydroxycorticosteroid determinations in Cushing's syndrome, 15
  17-ketosteroid excretion and gonadotropin administration (ab.), 950
Urine
  calculi of (ab.), 942
  concentration and potassium depletion (ab.), 950
  culture, evaluation of, 88

Valvular stenosis, pulmonary, and Brock type valvulotomy, 756
Valvulotomy
  Brock type, and pulmonary valvular stenosis, 756
  mitral, functional evaluation of, 745
  pulmonary, 53
Varidase and cerebral damage following circulatory arrest (ab.), 945
Vascular circulation in human forearm (ab.), 955
Vasoconstrictor activity and thrombocytosis (ab.), 949
Vasodepressor syncope, cardiac output in (ab.), 957
Vasomotor lability and hypoglycemia, 631
Vein, study of intact segment of (ab.), 943
Venesection and liver iron depletion (ab.), 951
Venomotor state in intact venous segment (ab.), 943
Venous
  pressure and loud presystolic sounds, 853
  return and cardiac decompensation (ab.), 948
Ventricular
  conduction disturbances, 834
  septal defect with aortic incompetence, 361
  septum, intact, and pulmonary stenosis, 53
Visceral manifestations of mucocutaneous leishmaniasis, 145
Vitamin
  B_{12} activity and leukemic serums (ab.), 951
    and aregenerative anemia (ab.), 941
    and degeneration of spinal cord, 896
    radioactive, absorption of, in megaloblastic anemia, 42
  deficiency and pernicious anemia (ab.), 955

X-ray diffraction analysis of gallstones, 383

The American Journal of Medicine

Editor ALEXANDER B. GUTMAN, M. D.
Professor of Medicine
COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK
DIRECTOR OF MEDICINE, THE MOUNT SINAI HOSPITAL, NEW YORK

ADVISORY BOARD

DAVID P. BARR, M.D., *Professor of Medicine*, Cornell University Medical College, *New York;* ARTHUR L. BLOOMFIELD, M.D., *Professor of Medicine*, School of Medicine, Stanford University, *San Francisco;* EUGENE A. STEAD, JR., M.D., *Professor of Medicine*, School of Medicine, Duke University, *Durham;* JOSEPH T. WEARN, M.D., *Professor of Medicine*, School of Medicine, Western Reserve University, *Cleveland.*

ASSOCIATE EDITORS

PAUL B. BEESON, M.D., *New Haven;* HERRMAN L. BLUMGART, M.D., *Boston;* EUGENE B. FERRIS, JR., M.D., *Atlanta;* HARRY GOLD, M.D., *New York;* A. MCGEHEE HARVEY, M.D., *Baltimore;* GEORGE H. HOUCK, M.D., *Palo Alto;* CHESTER S. KEEFER, M.D., *Boston;* WILLIAM S. MCCANN, M.D., *Rochester, N. Y.;* GEORGE R. MENEELY, M.D., *Nashville;* CARL V. MOORE, M.D., *St. Louis;* WALTER L. PALMER, M.D., *Chicago;* DEWITT STETTEN, JR., M.D., *Bethesda;* GEORGE W. THORN, M.D., *Boston;* WILLIAM S. TILLETT, M.D., *New York;* ROY H. TURNER, M.D., *New Orleans;* M. M. WINTROBE, M.D., *Salt Lake City;* JOHN B. YOUMANS, M.D., *Nashville.*

Volume XX
JANUARY TO JUNE
1956

THE AMERICAN JOURNAL OF MEDICINE, INC.
NEW YORK MCMLVI

COPYRIGHT, 1956
BY THE AMERICAN JOURNAL OF MEDICINE, INC.
All Rights Reserved

Printed in the United States of America

CONTENTS OF VOLUME XX
ORIGINAL ARTICLES

Interrelation of Citrate and Calcium Metabolism	*Harold E. Harrison*	1
Simmonds' Disease. Evaluation of Certain Laboratory Tests Used in Diagnosis	*Paul P. VanArsdel, Jr.* *Robert H. Williams*	4
Diagnostic Value of Plasma and Urinary 17-Hydroxycorticosteroid Determinations in Cushing's Syndrome	*Alan E. Lindsay* *Claude J. Migeon* *Charles A. Nugent* *Harold Brown*	15
Addison's Disease Associated with Histoplasmosis. Report of Four Cases and Review of the Literature	*K. R. Crispell* *William Parson* *James Hamlin* *Guy Hollifield*	23
Alterations in Thyroid I-131 Uptake, Basal Metabolic Rate and Serum Cholesterol Following Treatment of Hyperthyroidism with Radioactive Iodine. Value in Early Prediction of Success or Failure of Therapy	*Alvin L. Schultz* *Leslie Zieve*	30
Absorption of Radioactive Vitamin B_{12} in the Syndrome of Megaloblastic Anemia Associated with Intestinal Stricture or Anastomosis	*James A. Halsted* *Peter M. Lewis* *Marvin Gasster*	42
Pulmonary Stenosis with Intact Ventricular Septum. Correlation of Clinical and Physiologic Data, with Review of Operative Results	*Benjamin K. Silverman* *Alexander S. Nadas* *Martin H. Wittenborg* *Walter T. Goodale* *Robert E. Gross*	53
Atrial Flutter with 1:1 A-V Conduction. Report of Six Cases	*David Finkelstein* *Herman Gold* *Samuel Bellet*	65
Chronic Poliomyelitic Respirator Deaths	*Robert A. Blossom* *John E. Affeldt*	77
Evaluation of the "Positive" Urine Culture. An Approach to the Differentiation of Significant Bacteria from Contaminants	*Jay P. Sanford* *Cutting B. Favour* *Frances H. Mao* *J. Hartwell Harrison*	88
Hodgkin's Disease and Immunity	*W. Wilson Schier* *Arthur Roth* *George Ostroff* *Milton H. Schrift*	94
Treatment of Bromide Intoxication with Mercurial Diuretics	*Allen E. Hussar* *Howard L. Holley*	100
Subjective Response and Reaction to Sensation. The Reaction Phase as the Effective Site for Drug Action	*Henry K. Beecher*	107

The Genesis of Antibodies	*T. N. Harris* *Susanna Harris*	114
Acromegaly, Diabetes, Hypermetabolism, Proteinuria and Heart Failure		133
Visceral Manifestations of American Mucocutaneous Leishmaniasis	*Edward Shanbrom* *Richard Minton* *Charles Lester* *Juan L. Correa*	145
Psittacosis in Northern New Jersey. Human and Bird Transmitted	*Edward Singer* *Oscar Sussman* *James C. Barnett*	153
Postnephrectomy Renal Failure in a Patient with a Normal Preoperative Blood Non-Protein Nitrogen	*T. English McGeachy* *William Bloomer* *Arthur J. Merrill*	157
Molecular Events in Cardiac Failure	*Robert E. Olson*	159
Relationship of Immune Response to Group A Streptococci to the Course of Acute, Chronic and Recurrent Rheumatic Fever	*Gene H. Stollerman* *Arthur J. Lewis* *Irwin Schultz* *Angelo Taranta*	163
Relationship of Sydenham's Chorea to Infection with Group A Streptococci	*Angelo Taranta* *Gene H. Stollerman*	170
Epidemiologic Studies on Antibiotic-Resistant Strains of Micrococcus Pyogenes	*Robert I. Wise* *Caroline Cranny* *Wesley W. Spink*	176
Allergic Reactions in Sites Recurrently Infected with Hemolytic Streptococcus	*Franklin A. Stevens*	185
Blood Volume in Patients with Laennec's Cirrhosis of the Liver as Determined by Radioactive Chromium-Tagged Red Cells	*Seymour Eisenberg*	189
Splenomegaly in Sickle Cell Anemia	*R. Janet Watson* *Herbert C. Lichtman* *Henry D. Shapiro*	196
Survival of Diabetic Patients after Myocardial Infarction	*R. F. Bradley* *J. W. Bryfogle*	207
Production of Renal Ischemia and Proteinuria in Man by the Adrenal Medullary Hormones	*S. Edward King* *Capt. David S. Baldwin*	217
Metabolic Observations during the Forced Feeding of Patients with Cancer	*A. Raymond Terepka* *Christine Waterhouse*	225
The Porphyrins and Porphyria. A Review of Eighty-one Cases	*William J. Martin* *Frank J. Heck*	239
Types and Distribution of Antibodies	*William J. Kuhns*	251
Central Nervous System Disease Characterized by Low Spinal Fluid Sugar		275
Brief Psychotherapy of a Patient with Headache and Endometriosis		286

Diffuse Lymphosarcomatosis of the Central Nervous System Simulating Infectious Polyneuritis	*Lt. Col. Roy E. Clausen, Jr.* *Lt. Col. Arthur F. Lincoln* *Capt. Henry K. Silberman*	292
Symmetric Peripheral Gangrene Complicating Acute Myocardial Infarction	*Robert T. Cotton* *D. R. Bedford*	301
Hamman-Rich Syndrome. Report of a Case Diagnosed Antemortem by Lung Biopsy and Successfully Treated with Long-term Cortisone Therapy	*C. T. Pinney* *H. William Harris*	308
Familial Non-hemolytic Icterus	*Waddy G. Baroody* *Maj. Richard T. Shugart*	314
On the "Turnover" of Plasma Proteins	*J. Murray Luck*	317
Ebstein's Disease	*James W. Brown* *Donald Heath* *William Whitaker*	322
Mechanism of A-V Arrhythmias. With an Electronic Analogue of the Human A-V Node	*Robert P. Grant*	334
Antemortem Diagnosis of Syphilitic Aneurysm of the Aortic Sinuses. Report of Nine Cases	*Charles W. Merten* *Nathaniel Finby* *Israel Steinberg*	345
Ventricular Septal Defect with Aortic Incompetence Simulating Patent Ductus Arteriosus	*Paul Winchell* *Fouad Bashour*	361
Clinical and Pathologic Significance of Atheromatous Embolization, with Emphasis on an Etiology of Renal Hypertension	*Fred P. Handler*	366
Idiopathic Pulmonary Hemosiderosis	*J. R. Browning* *John D. Houghton*	374
Biliary Tract Studies. I. X-ray Diffraction Analysis of Gallstones; Correlation with Occurrence of Microspheroliths in Bile	*Kerrison Juniper, Jr.* *William E. Woolf*	383
Therapy of the Malignant Lymphomas		
I. A Study of 116 Cases	*Charles A. Hall*	392
II. A Review	*Kenneth B. Olson*	399
Clinical Trial of Glaucarubin in Treatment of Amebiasis	*Efrén C. del Pozo* *Manuel Alcaraz*	412
Serologic Tests for Inflammation. Serum Complement, C-reactive Protein and Erythrocyte Sedimentation Rate in Myocardial Infarction	*Adolph J. Boltax* *Edward E. Fischel*	418
Delayed Type of Allergic Inflammatory Response	*H. Sherwood Lawrence*	428
Disorders of Renal Tubular Function		448
Arthritis, Polymyositis and Polyneuritis		462
Isolated Congenital Bicuspid Pulmonary Valve. Clinical and Pathologic Study	*Amasa B. Ford.* *Herman K. Hellerstein* *Colin Wood.* *Hugh B. Kelly*	474

Serologic Reactions in Rheumatoid Arthritis	*Wallace Epstein* *Charles Ragan*	487
The Hemagglutination Test for Rheumatoid Arthritis. III. Clinical Evaluation of the Sheep Erythrocyte Agglutination (S.E.A.) Test and the Gamma Globulin (FII) Tests	*Abraham S. Jacobson* *William H. Kammerer* *Julius Wolf* *Wallace V. Epstein* *George Heller*	490
Agglutination and Inhibition by Serum Globulin in the Sensitized Sheep Cell Agglutination Reaction in Rheumatoid Arthritis	*Morris Ziff* *Patricia Brown* *Joseph Lospalluto* *Jacques Badin* *Currier McEwen*	500
Synovial Specimens Obtained by Knee Joint Punch Biopsy. Histologic Study in Joint Diseases	*Henry A. Zevely* *A. James French* *William M. Mikkelsen* *Ivan F. Duff*	510
A Clinical, Physiologic and Biochemical Study of Patients with Malignant Carcinoid (Argentaffinoma)	*Albert Sjoerdsma* *Herbert Weissbach* *Sidney Udenfriend*	520
Essential Cryoglobulinaemia. Review of the Literature and Report of a Case Treated with ACTH and Cortisone	*Robert Volpé* *Alan Bruce-Robertson* *A. Almon Fletcher* *W. Bruce Charles*	533
Insulin-Zinc Suspensions. Further Studies, with Emphasis on Lente Insulin	*Joseph L. Izzo*	554
Cryo- and Macroglobulinemia. Electrophoretic, Ultracentrifugal and Clinical Studies	*Ian R. Mackay* *Nils Eriksen* *Arno G. Motulsky* *Wade Volwiler*	564
Monocytic Leukemia	*Charles M. Sinn* *Frederick W. Dick*	588
Diagnostic Methods for Allergic Diseases	*William B. Sherman*	603
Recurrent Burning Retrosternal Pain		612
Cryoproteinemia: An Immunologic Phenomenon? Electrophoretic Analysis of Serum Proteins of a Patient with Cold Allergy	*Z. T. Wirtschafter* *D. W. Williams* *E. C. Gaulden*	624
Studies on a Patient with Severe Hyperinsulinism Treated with Cortisone for Three Years	*Herbert Gershberg* *Elaine P. Ralli*	631
Pericardial Effusion in Generalized Scleroderma	*Jay I. Meltzer*	638
Infectious Mononucleosis of the Central Nervous System. Demonstration of Atypical Lymphocytes in the Cerebrospinal Fluid	*Leo E. Hollister* *George H. Houck* *William A. Dunlap*	643
Dextroposition of the Heart Simulating Congenital Dextrocardia	*Werner J. Hollendonner* *Bernard H. Pastor*	647
Foreword	*Rulon W. Rawson*	651
Pathways of Iodine Metabolism	*Solomon A. Berson*	653

Recent Progress in the Physiology and Biochemistry of Thyroid Hormones	*Raymond Michel*	670
Physiologic Concepts in the Diagnosis and Treatment of Graves' Disease	*Brown M. Dobyns*	684
Physiologic Considerations in the Genesis and Management of Nodular Goiter	*Selwyn Taylor*	698
Physiologic Concepts in the Genesis and Management of Thyroid Tumors	*Martin Sonenberg*	710
The Role of Radioactive Iodine in the Diagnosis of Thyroid Disease	*J. E. Rall*	719
Physiology and Treatment of Myxedema	*Samuel P. Asper, Jr.* *John G. Wiswell*	732
Functional Evaluation of Mitral Valvulotomy. Superiority of the Treadmill Exercise Tolerance Test to Clinical and Resting Hemodynamic Evaluations in Selecting Patients	*R. A. Bruce* *K. A. Merendino* *J. J. Pampush* *G. G. Bergy* *L. L. Brock*	745
Pulmonary Valvular Stenosis with Intact Ventricular Septum. Results of the Brock Type Valvulotomy	*C. Walton Lillehei* *Paul Winchell* *Paul Adams* *Ivan Baronofsky* *Forrest Adams* *Richard L. Varco*	756
A Long-Term Study of the Effect of Crude Rauwolfia Serpentina and of Its Alseroxylon Fraction in Patients with Hypertension	*Robert S. Green* *Dominick Davolos*	760
Therapeutic Activity of Desiccated Thyroid Substance, Sodium L-Thyroxine and D,L-Triiodothyronine. A Comparative Study	*Thomas H. McGavack* *Hellmuth K. Reckendorf*	774
Bronchial Asthma	*Francis C. Lowell*	778
Potassium Depletion by Enemas	*Marcelle F. Dunning* *Fred Plum*	789
Scleroderma of the Kidneys	*Charles A. Hannigan* *Margaret Hopkins Hannigan* *Edwin L. Scott*	793
Congenital Hemorrhagic Diathesis of the Prothrombin Complex	*T. Newcomb* *M. Matter* *L. Conroy* *Q. B. DeMarsh* *C. A. Finch*	798
Hemolytic Anemia Due to Quinidine: Observations on Its Mechanism	*A. L. Freedman* *P. S. Barr* *E. A. Brody*	806
The Levels of Disorganization	*DeWitt Stetten, Jr.*	817

Studies on Myocardial Metabolism. VI. Myocardial Metabolism in Congestive Failure	*J. M. Blain*, *H. Schafer*, *A. L. Siegel*, *R. J. Bing*	820
Mechanisms of QRS Complex Prolongation in Man. Left Ventricular Conduction Disturbances	*Robert P. Grant*, *Harold T. Dodge*	834
Loud Presystolic Sounds over the Jugular Veins Associated with High Venous Pressure	*William Dock*	853
Pendular Motion of the Mediastinum	*Philip Samet*, *William Anderson*	860
Congenital Heart Block	*Ephraim Donoso*, *Eugene Braunwald*, *Sidney Jick*, *Arthur Grishman*	869
Relationship of Portal Hypertension to Ascites in Laennec's Cirrhosis	*William J. Eisenmenger*, *William F. Nickel*	879
Studies in Ammonia Metabolism. I. Ammonia Metabolism and Glutamate Therapy in Hepatic Coma	*B. Eiseman*, *W. Bakewell*, *G. Clark*	890
Subacute Combined Degeneration of the Spinal Cord. Current Concepts of the Disease Process. Value of Serum Vitamin B_{12} Determinations in Clarifying Some of the Common Clinical Problems	*Maurice Victor*, *Arnold A. Lear*	896
Treatment of Barbiturate Poisoning with or without Analeptics	*James E. Eckenhoff*, *Willy Dam*	912
Life Stress and Allergy	*Stewart Wolf*	919
Hypertension, Proteinuria and Edema		929
Southern Society for Clinical Research—Abstracts of Papers Presented at the Tenth Annual Meeting, New Orleans, Louisiana, January 21, 1956		941
Immunologic Agranulocytosis Due to Mercurial Diuretics	*B. J. Koszewski*, *T. F. Hubbard*	958
Combined Bacillary and Amebic Ulcerative Colitis Associated with Atypical Pneumonitis and Shigella-Positive Sputum	*Edward A. Raffensperger*	964
Effect of Intramuscular Heparin on Antibodies in Idiopathic Acquired Hemolytic Anemia	*Karl L. Roth*, *Abraham M. Frumin*	968

A RESEARCH MILESTONE

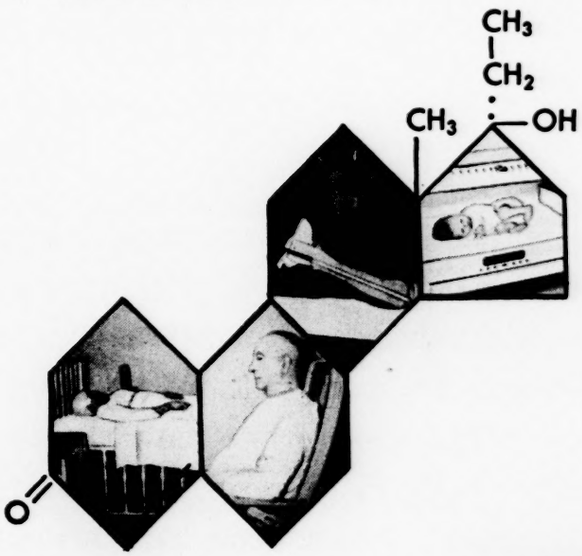
Nilevar*

(BRAND OF NORETHANDROLONE)

Searle's New and Practical Steroid Specifically for Protein Anabolism–

It has long been recognized that a substance which would promote protein anabolism would be of inestimable value in therapy. The androgens have this property, but unfortunately they also exert actions on secondary sex characteristics. These effects are commonly undesirable in therapeutic programs.

THE FIRST STEROID WITH ANABOLIC SPECIFICITY—Nilevar, the newest Searle Research development, therefore, meets a long desired clinical need because Nilevar presents the first steroid primarily anabolic for protein synthesis. Moreover, Nilevar is without prominent androgenic effects (only about one-sixteenth of that exerted by the androgens).



OBJECTIVE AND SUBJECTIVE RESPONSE—Orally effective, Nilevar therapy is characterized by retention of nitrogen, potassium, phosphorus and other electrolytes in ratios indicative of protein anabolism. Moreover, subjectively the patient observes an increase in appetite and sense of well-being.

WELL TOLERATED—Nilevar has an extremely low toxicity. Laboratory animals fail to show toxic effects after six months of continuous administration of high dosages. Nilevar should not be administered to patients with prostatic carcinoma. Nausea or edema may be encountered infrequently. Slight androgenicity may be evidenced on high dosage or in particularly responsive individuals.

MAJOR INDICATIONS—Preparation for and recovery from surgery; supportive treatment of serious illnesses (pneumonia, poliomyelitis, carcinomatosis, tuberculosis); recovery from severe trauma and burns; decubitus ulcers; care of premature infants.

DOSAGE—The daily *adult* dose is three to five Nilevar tablets (30 to 50 mg.) but up to 100 mg. may be administered. For *children* the average daily dose is 1 to 1.5 mg. per kilogram of body weight; individual dosages depend on need and response to therapy.

SUPPLY—Nilevar is available in uncoated, unscored tablets of 10 mg. G. D. Searle & Co., Research in the Service of Medicine.

*Trademark of G. D. Searle & Co.

SEARLE

IN WOMEN,

the preferred broad spectrum antibiotic preparation is

MYSTECLIN

STECLIN-MYCOSTATIN (SQUIBB TETRACYCLINE-NYSTATIN)

Usual broad spectrum antibiotic therapy may be followed by vaginal moniliasis. Mysteclin supplies well tolerated broad spectrum therapy without subsequent vaginal moniliasis.*

*Stone, M. L., and Mersheimer, W. L.: "Comparison of side effects of tetracycline and tetracycline combined with nystatin." Antibiotics Annual 1955-56, New York, Medical Encyclopedia Inc., 1956, p. 862.

Vaginal moniliasis following antibiotic therapy

Oral antibiotic therapy may cause an overgrowth of monilia in the vagina, producing vaginal moniliasis with vulvar pruritus and vaginal discharge. All women are susceptible, but this complication is especially frequent in women who are pregnant or diabetic. In many cases, the woman fails to inform the physician through embarrassment or failure to relate the condition to preceding antibiotic therapy.

'MYSTECLIN' ®, 'STECLIN' ® AND 'MYCOSTATIN' ® ARE SQUIBB TRADEMARKS

SQUIBB

vaginal moniliasis: an increasingly common complication of antibiotic therapy

"... wide use of penicillin and broad spectrum antibiotics, with resultant disturbance of vaginal bacteriology has increased markedly the incidence of yeast and fungus infections of the vagina.... Before advent of the wonder drugs, relationship of trichomonas to monilia was roughly four to one in the usual office practice. Within the past eight years the ratio has been reversed with three monilia problems to one of trichomonas."

Lee, A. F. and Keifer, W. S.:
Northwest Med. 53:1227 (Dec.) 1954.

"Vaginal moniliasis ... is quite common and the incidence may well have been increased following the extensive use of the broad-spectrum drugs or prolonged oral use of penicillin."

Welch, H.: Editorial,
Antibiotic Med. 2:79 (Feb.) 1956.

MYSTECLIN

the only broad spectrum antibiotic preparation that:

1: provides the antibacterial activity of tetracycline and

2: protects the patient against monilial superinfection

Each Mysteclin capsule contains 250 mg. Steclin (Squibb Tetracycline) Hydrochloride, a well tolerated broad spectrum antibiotic, and 250,000 units Mycostatin (Squibb Nystatin), the first well tolerated antibiotic active against fungi. Minimum adult dosage: 1 capsule q.i.d. Supply: Bottles of 16 and 100.

also available: MYSTECLIN Half Strength Capsules (125 mg. Steclin Hydrochloride and 125,000 units Mycostatin): Bottles of 16 and 100.

A PARTIAL LIST OF INDICATIONS FOR MYSTECLIN

When caused by tetracycline-susceptible organisms, the following conditions are among those which may be expected to respond to Mysteclin:

- Abscess
- Bronchiectasis
- Bronchitis
- Bronchopneumonia
- Burns, Infected
- Cellulitis
- Cervicitis
- Chancroid
- Colitis
- Cystitis
- Diarrheas, Infectious
- Dysentery, Amebic
- Dysentery, Bacillary
- Empyema
- Endocarditis, Bacterial
- Epididymitis
- Furunculosis
- Gastroenteritis
- Gonorrhea
- Granuloma Inguinale
- Klebsiella Pneumonia
- Laryngitis
- Lymphadenitis
- Lymphangitis
- Lymphogranuloma Venereum
- Mastoiditis
- Meningitis
- Metritis
- Osteomyelitis
- Otitis Media
- Peritonitis
- Pertussis
- Pharyngitis
- Pneumonia
- Psittacosis
- Pyelonephritis
- Q Fever
- Rocky Mountain Spotted Fever
- Salpingitis
- Scarlet Fever
- Scrub Typhus
- Sepsis, Puerperal
- Septic Sore Throat
- Septicemia
- Sinusitis
- Skin Graft Infections
- Surgical Prophylaxis
- Tonsillitis
- Tracheobronchitis
- Tularemia
- Typhus
- Urethritis
- Vesiculitis
- Wounds, Infected

It is impossible to predict with certainty in which patients clinical moniliasis may develop as a result of broad spectrum antibiotic therapy.

However, the added protection afforded by Mysteclin against monilial superinfection is *especially* important when antibiotic therapy must be prescribed in high dosage or for prolonged periods.

It is also particularly important in women; in debilitated, elderly, or diabetic patients; in infants (particularly prematures); in patients for whom concomitant cortisone or related steroid therapy is prescribed; and in individuals who have developed a monilial complication on previous broad spectrum therapy.

BRING YOUR PATIENT'S **HIDDEN INFLAMMATION**

TO LIGHT WITH

C·R·P·A®

(C-reactive Protein Antiserum, Schieffelin)

- **C-Reactive protein in serum only when inflammation exists.**
- **Unlike E.S.R., no "Normal" range... either negative or positive.**
- **No false positives.**
- **Simpler . . . faster . . . more reliable aid to diagnosis.**
- **Quantity of precipitate reflects severity of condition . . . Precipitate diminishes as therapy reduces inflammation.**

Both venous blood and blood obtained by the "finger tip technique" (punctured as for blood count) can be used with equally reliable results. To make the test procedure fast and convenient a new compact C.R.P.A. Test Kit is now available; it contains C.R.P.A., CRP-Positest control solution, capillary tubes, test rack, and illustrated directions.

COMPLETE LITERATURE ON C.R.P.A. IN DETECTION OF RHEUMATIC DISEASES, MYOCARDIAL INFARCTION, AND MANY OTHER DISEASE STATES ON REQUEST.

Supplied:

TEST KIT *(For the complete procedure)*

C.R.P.A. . . . 1 ml. vials (80-110 determinations)

CRP-POSITEST* . . . 0.5 ml. vials
(Standardized test-control solution of C-Reactive Protein)

CAPILLARY TUBE RACK

CAPILLARY TUBES
(Two sizes) . . . 0.8 mm ID – 1.5 mm ID

*Trademark

Schieffelin
QUALITY INTEGRITY SERVICE

Schieffelin & Co.

New York 3, N. Y. • Since 1794

Laboratory Products Division

In Canada: William Sofin & Co., Ltd., Montreal 25, Quebec

treat adrenocortical insufficiency

without the
difficulties
of
implants

without the
unpleasantness
of daily
injections

with a SINGLE injection a month

Percorten®

trimethylacetate

(desoxycorticosterone trimethylacetate CIBA)

Percorten trimethylacetate, developed after more than 3 years of research by CIBA, provides expedient, lasting hormonal support for the patient with adrenocortical hypofunction . . . avoiding both the uncertainty of surgical implantation and the vexation of daily injections. With once-a-month therapy, a single injection will produce prolonged activity without acute signs of overdosage.[1]

Multiple-dose Vials, 4 ml., containing 25 mg. Percorten trimethylacetate per ml. as an aqueous microcrystalline suspension for intramuscular use only.

1. Frawley, T. F., and Forsham, P. H.: J. Clin. Endocrinol. *11*:772 (July) 1951.

CIBA
SUMMIT, N. J.

2/233314

Only Meat . . . is Meat

Suppose we suddenly found ourselves in a "Brave New World," in which all the rich protein, the B vitamins (including the important B_{12}), the minerals, and all the other nutrients of a juicy steak or a succulent pork chop could be compressed into a capsule. Suppose we were to take one or two such capsules each day. What would happen?

Would we be just as healthy? Would we be as happy?

There is something about man's wish for meat that cannot be satisfied by chemical or mathematical analyses. The feeling of satisfaction, the downright enjoyment of biting into and chewing, the pleasurable effect of having eaten well . . . all these make meat more than just an impressive list of essential nutrients. Long before man knew anything about the science of nutrition he knew meat was part and parcel of his health and his joy of eating and of living.

Other foods may be fortified and enriched, *but none can ever take the place of meat.*

Only meat is meat.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
Main Office, Chicago . . . Members Throughout the United States

PATIENTS ON "MEDIATRIC" CAN EXPECT A HEALTHIER, HAPPIER "SECOND FORTY YEARS"

Steroid-Nutritional Therapy Provides a Constructive Approach in Preventive Geriatrics

"MEDIATRIC"®

AYERST LABORATORIES
New York, N.Y. • Montreal, Canada
5659

TRI-SYNAR
provides optimal spasmolysis

NOW NEW

TRI-SYNAR PLUS

adds relaxation of mental tension to optimal spasmolysis—

... especially in the control of primary dysmenorrhea and gastrointestinal spasm—

Tri-Synar Plus provides a triple attack—musculotropic, anticholinergic and antihistaminic—against smooth muscle spasm, plus the relaxation of mental tension and smooth muscle produced by the barbiturate components.

Each Tri-Synar Plus tablet contains:

Powdered Extract of Belladonna*	4.1 mg.
Phenyltoloxamine Dihydrogen Citrate	20.0 mg.
Ethaverine Hydrochloride	12.5 mg.
Secobarbital Sodium	6.075 mg.
Pentobarbital Sodium	6.075 mg.
Butabarbital Sodium	2.025 mg.
Phenobarbital	2.025 mg.

*The amount of belladonna is equivalent to 2.5 minims of tincture of belladonna, U.S.P.

in bottles of 100 tablets

THE ARMOUR LABORATORIES

filmtab

Nembu-Serpïm

TRADEMARK

round-the-clock sedation plus tranquilization

The combination of 30 mg. (½ gr.) Nembutal Calcium (Pentobarbital Calcium) and 0.25 mg. reserpine in each tiny Nembu-Serpin Filmtab provides longer-lasting sedation—without drowsiness— than Nembutal alone, plus a more rapid onset of tranquilizing effect than reserpine alone.

- short-acting Nembutal quickly induces drowsiness at bedtime, followed by refreshing sleep.
- longer-acting reserpine calms patients through the following days, yet they keep their drive and energy.

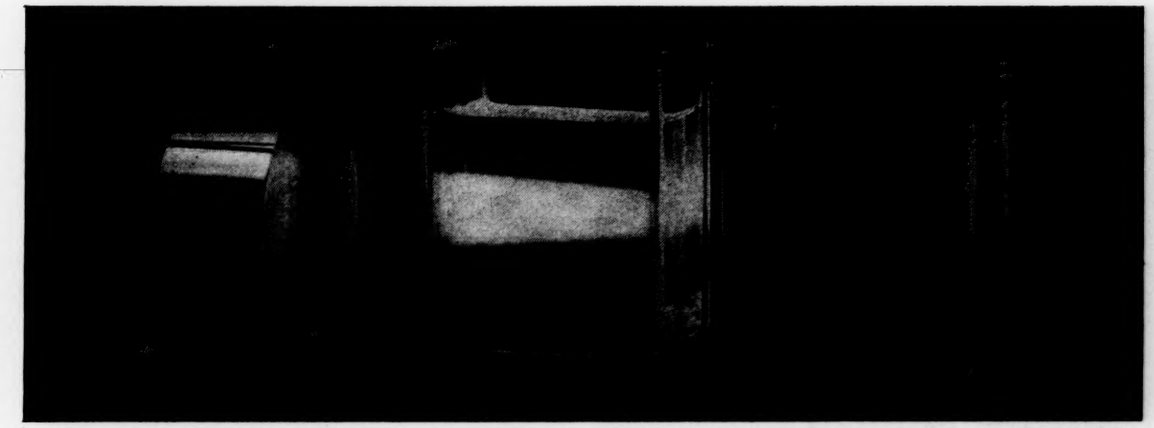
Faster-acting—no waiting for cumulative response. Anxiety and hypertension patients experience almost immediate relief as Nembu-Serpin's sedative-tranquilizing action rapidly takes effect.

Smaller dosages—fewer side effects. Small dosages make side effects rare, medication economical, dosage schedules simple. Just one Nembu-Serpin Filmtab at bedtime will calm the worries of most anxiety patients. In bottles of 100 and 500 Filmtabs.

Abbott

©Film-sealed tablets.

THIRD REPORT



ANOTHER HIGHLIGHT ON LECITHIN – A NATURAL PHOSPHATIDE

Phosphatides – Clearing Agents of Blood Plasma

Phosphatides have been found in all vegetable and animal cells. There seems little doubt that they are part of the basic structure of protoplasm and also enter into cell metabolism. The most abundantly found phosphatides are the lecithins, whose surface active properties, when combined with proteins and carbohydrates, play an important role as physiologic emulsifiers of fats and oils.[1]

The following considerations highlight the importance of *adequate lecithin plasma concentrations.*

Phosphatides together with cholesterol are found in plasma in combination with proteins and circulate as lipoproteins.[2] The phosphatides in plasma protein are believed to be highly essential for the stability of the complex colloidal system represented by blood plasma.[3] A phosphatide content of 30% or more seems necessary to keep the plasma clear and non-lipemic;[2] lower concentrations will cause the plasma to remain cloudy. (In human plasma lecithin makes up about 80% of the phosphatides present; others are sphingomyelin and cephalin.[2]) A constantly cloudy, lipemic serum can be considered a sign of disturbed fat metabolism, which has been incriminated in the pathogenesis of many serious disturbances. Research on lecithin's potentially useful role in the management of the more complicated forms of deranged lipid and cholesterol metabolism – as in essential hyperlipemia, idiopathic familial hypercholesteremia, xanthomatosis and diabetes – is now being actively conducted. If you are interested in the progress of this research or if you desire to have clinical trial supplies, won't you write to us?

An excellent source of lecithin is Glidden's "RG" Oil-free Soya Lecithin, a highly purified extract containing a minimum of 95% phospholipids. It is packed in a specially designed 8 oz. container to maintain its purity and freshness and is available at your drugstore.

Investigators of lecithin have used quantities from 7.5 to 30 grams daily in divided doses (3 teaspoonfuls equal 7.5 grams).

Administration: "RG" Lecithin is presented in palatable granules which may be taken plain, in milk, in orange juice or other citrus juice, or sprinkled on cereal.

Literature available on request.

Bibliography: 1. West, E. S., and Todd, W. R.: Textbook of Biochemistry, New York, The Macmillan Company, 1952, p. 184. • 2. Drill, V. A.: Pharmacology in Medicine, New York, McGraw-Hill Book Company, Inc., 1954, p. 64/6. • 3. Ahrens, E. H., Jr., and Kunkel, H. G.: J. Exper. Med. *90*:409 (Nov. 1) 1949.

GLIDDEN RG® LECITHIN

THE GLIDDEN COMPANY • CHEMURGY DIVISION
1825 North Laramie Avenue, Chicago 39, Illinois

QUALITY Glidden PRODUCTS

PROVEN PAIN CONTROL

with safety

GRADATIONS OF ANALGESIA

'TABLOID' 'EMPIRIN' COMPOUND®
Acetophenetidin gr. 2½, Acetylsalicylic Acid gr. 3½, Caffeine gr. ½

'TABLOID' 'EMPIRIN' COMPOUND
with **CODEINE PHOSPHATE gr. ⅛, No. 1** (N)

'TABLOID' 'EMPIRIN' COMPOUND
with **CODEINE PHOSPHATE gr. ¼, No. 2** (N)

'TABLOID' 'EMPIRIN' COMPOUND
with **CODEINE PHOSPHATE gr. ½, No. 3** (N)

'TABLOID' 'EMPIRIN' COMPOUND
with **CODEINE PHOSPHATE gr. 1, No. 4** (N)

(N) subject to Federal Narcotic Law

BURROUGHS WELLCOME & CO. (U.S.A.) INC.
Tuckahoe, N. Y.

fresh mixed

FOLBESYN*

VITAMINS LEDERLE

B+C COMPLEX

assures full potency

Separate packaging of dry vitamins and diluent (mixed immediately before injection) assures the patient a more effective dose. May also be added to standard IV solutions.

Dosage: 2 cc. daily.

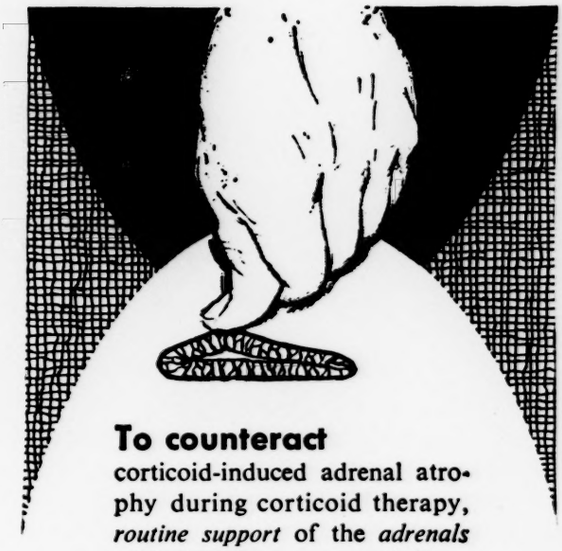
Each 2 cc. dose contains:

Thiamine HCl (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	50 mg.
Pyridoxine HCl (B_6)	5 mg.
Sodium Pantothenate	10 mg.
Ascorbic Acid (C)	300 mg.
Vitamin B_{12}	15 mcgm.
Folic Acid	3 mg.

Lederle

LEDERLE LABORATORIES DIVISION
AMERICAN Cyanamid COMPANY
PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.



To counteract
corticoid-induced adrenal atrophy during corticoid therapy, *routine support* of the *adrenals with ACTH is recommended.*

THIS IS THE PROTECTIVE DOSAGE RECOMMENDATION FOR COMBINED CORTICOID-ACTH THERAPY

- When using *prednisone* or *prednisolone:* for every 100 mg. given, inject approximately 100 to 120 units of HP* ACTHAR *Gel.*
- When using *hydrocortisone:* for every 200 to 300 mg. given, inject approximately 100 units of HP* ACTHAR *Gel.*
- When using *cortisone:* for every 400 mg. given, inject approximately 100 units of HP*ACTHAR *Gel.*

Discontinue administration of corticoids on the day of the HP*ACTHAR *Gel* injection.

HP*ACTHAR® *Gel*
(IN GELATIN)

The Armour Laboratories brand of purified adrenocorticotropic hormone—corticotropin (ACTH)

*Highly Purified

Unsurpassed in Safety and Efficacy
More than 42,000,000 doses of ACTH have been given

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY
KANKAKEE, ILLINOIS

PROVEN PAIN CONTROL
with sedation

GRADATIONS OF ANALGESIA with light sedation

'EMPIRAL'®

Phenobarbital	gr. ¼
Acetophenetidin	gr. 2½
Acetylsalicylic Acid	gr. 3½

'CODEMPIRAL'® No. 2(N)

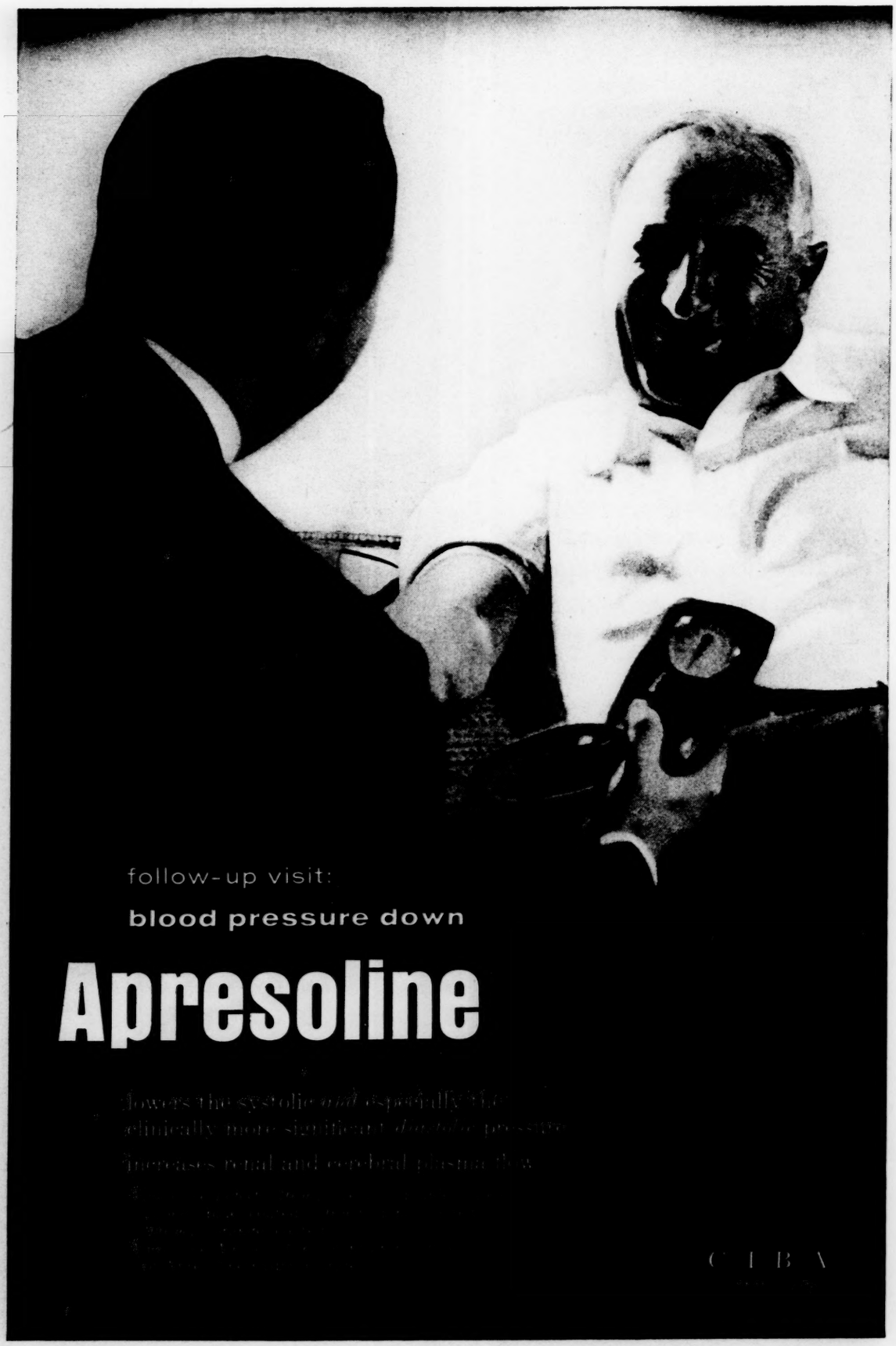
Codeine Phosphate	gr. ¼
Phenobarbital	gr. ¼
Acetophenetidin	gr. 2½
Acetylsalicylic Acid	gr. 3½

'CODEMPIRAL'® No. 3(N)

Codeine Phosphate	gr. ½
Phenobarbital	gr. ¼
Acetophenetidin	gr. 2½
Acetylsalicylic Acid	gr. 3½

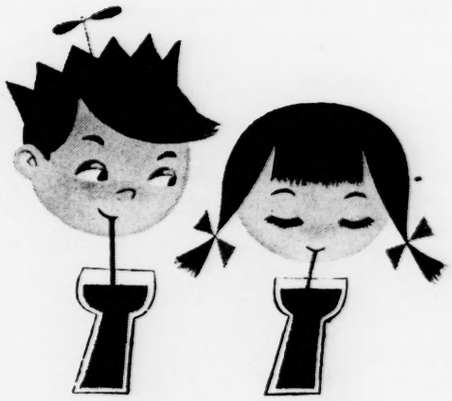
(N) subject to Federal Narcotic Law

BURROUGHS WELLCOME & CO. (U.S.A.) INC.
Tuckahoe, N. Y.


follow-up visit:
blood pressure down
Apresoline
CIBA

It's a date—

...among other things...which distinguishes Vi-Penta Drops 'Roche.' Since all multivitamin solutions tend to lose strength in time, Vi-Penta® Drops are dated to assure full label potency. Just 0.6 cc daily provides required amounts of A, C, D and B vitamins (including B_6), and you'll find that both mothers and youngsters like them because they're easy to give and easy to take... Hoffmann - La Roche Inc.
Nutley 10, N. J.



HEDULIN®

(Phenindione Walker)

". . . . . *it is our feeling that, at present, this [phenindione] is the oral anticoagulant of choice.*"

Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129-35, 1955.

". . . . . *phenindione seems to be a more satisfactory anticoagulant at this time.*"

Wood, J. E., Jr.; Beckwith, J. R., and Camp, J. L.: J.A.M.A. 159:635, 1955.

HEDULIN permits dependable prothrombin control with little risk of dangerous fluctuation

(Not a Coumarin Drug)

DOSAGE 4 to 10 tablets (200 to 500 mg.) initially, half in the morning, and half at night; maintenance dosage (on basis of prothrombin determination daily for first 3 days), 50 to 100 mg. daily, divided as above.

AVAILABLE on prescription through all pharmacies in original bottles of 100 and 1,000 scored tablets (50 mg. each).

HEDULIN is not cumulative in effect — provides greater uniformity of action and ease of maintenance.

HEDULIN is rapidly excreted — therapeutic effect dissipated within 24-48 hours, if withdrawal becomes necessary.

HEDULIN acts promptly — producing therapeutic prothrombin levels in 18-24 hours.

HEDULIN requires fewer prothrombin determinations—only one every 7-14 days after maintenance dose is established.

HEDULIN's anticoagulant action is rapidly reversed by vitamin K_1 emulsion.

WRITE FOR LITERATURE AND TRIAL SUPPLIES

Walker LABORATORIES, INC.

MOUNT VERNON, NEW YORK, U.S.A.

S & H—7043—SS1201

NEW 6th edition with 18 bi-monthly modern drugs supplements $15

The only three-year reference service of its kind with complete, authoritative data on new ethical drugs now completely revised in this new, "better than ever", 6th Edition. Prescription products, narcotics and exempt-narcotics are indicated for the first time. Here is your source for latest composition, action, uses, supply, dosage—also cautions and contraindications of thousands of new drugs.

HANDSOMELY BOUND IN RED FABRICOID CONTAINS over 1500 PAGES, SIZE 6" x 9¼" x 2¼"

COMPLETE WITH GENERIC NAME INDEX AND SELF-PRONOUNCING DRUG LISTINGS

- *Over 50,000 Physician, Pharmacist, Institution purchasers*
- *Now required by Michigan State Board of Pharmacy*
- *Recognized as leading reference text by College and University Schools of Pharmacy*
- *97.2% subscribers who receive it . . . use it*
- *89.8% keep it within finger-tip reach*

MAIL THIS COUPON NOW

DRUG PUBLICATIONS, INC.
49 West 45th Street, New York 36, N. Y.

Enclosed is the sum of fifteen dollars ($15.00** U.S.A.) for which please send me postpaid the Sixth Edition of the MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC INDEX plus the bi-monthly supplementary service, MODERN DRUGS. Binder for supplements—$2.50 extra.

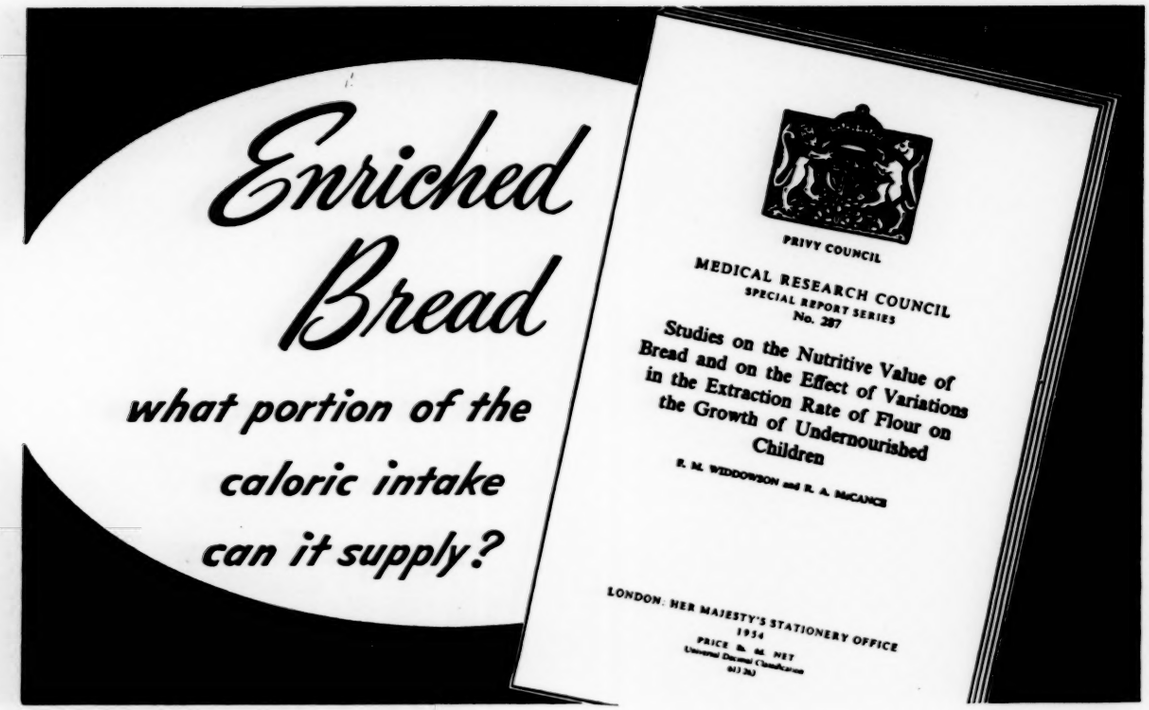
NAME _____

ADDRESS _____

CITY _____ ZONE _____ STATE _____

**Foreign $18.00 **Includes three-year supplementary service at $3 per year.

M 66


Enriched Bread
what portion of the caloric intake can it supply?
PRIVY COUNCIL
MEDICAL RESEARCH COUNCIL
SPECIAL REPORT SERIES
No. 287
Studies on the Nutritive Value of Bread and on the Effect of Variations in the Extraction Rate of Flour on the Growth of Undernourished Children
R. M. WIDDOWSON and R. A. McCANCE
LONDON: HER MAJESTY'S STATIONERY OFFICE
1954

A striking observation was made in a recently reported nutrition study. Undernourished children in a German orphanage, placed on diets providing a high percentage of their total calories in the form of bread, not only improved in health, but "in spite of the simple diet provided" gained in weight and increased in height at a highly satisfactory rate.*

The children received daily supplements of vitamin A, 2000 I.U., vitamin D, 1000 I.U., and ascorbic acid, 25 mg.

In the words of the investigators: "One of the most striking findings, . . . and perhaps the most unexpected one, was the remarkable way in which the general condition of all the children . . . improved . . ."

"Probably the most important finding concerns the high nutritive value of wheat in any of the forms customarily consumed by man. . . . [The diets fed] provided undernourished children aged 5-15 years with all the nutrients required for a high rate of growth and development for a period of 18 months."

Enriched bread, made from 70 per cent extraction flour and very similar to enriched bread sold in the United States, was among the breads used. While the diets used in this study are not justified in this country with its abundant food supply, hence do not merit consideration for applicability here, they nevertheless serve to emphasize again the high nutritional value of enriched bread.

*Widdowson, E. M., and McCance, R. A.: Studies on the Nutritive Value of Bread and on the Effect of Variations in the Extraction Rate of Flour on the Growth of Undernourished Children, Medical Research Council, Special Report Series, No. 287, London, Her Majesty's Stationery Office, 1954.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

AMERICAN BAKERS ASSOCIATION 20 North Wacker Drive • Chicago 6, Illinois

What do you want in an analgesic?

Percodan®*

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC)

FOR PAIN

Better than codeine plus APC

speed acts faster than codeine plus APC—usually within 15 minutes[1, 2]

duration relieves pain longer than codeine plus APC—usually for 6 hours with virtual freedom from constipation[1, 2]

Average adult dosage, 1 tablet q. 6 h. Supplied as scored, yellow oral tablets. May be habit-forming. Literature? Write—

Endo®

ENDO LABORATORIES INC. Richmond Hill 18, New York

1. Blank, P., and Boas, H.: Ann. West. Med. & Surg. 6:376, 1952.
2. Piper, C. E., and Nicklas, F. W.: Indust. Med. 23:510, 1954.

*U.S. Pat. 2,628,185

clinically proved in many common infections[1-60]

Hemolytic streptococcal infections

Pharyngitis/Tonsillitis/Sinusitis
Otitis media/Mastoiditis
Scarlet fever/Lymphadenitis/Erysipelas

Staphylococcal infections/Pneumococcal infections/Gonococcal infections/ Vincent's Infection/Prevention of streptococcal infection in individuals with a history of rheumatic fever/ Prevention of secondary infection due to penicillin-susceptible organisms

in dosage of just 1 or 2 tablets t.i.d.

and is far less costly than other penicillin salts

Pentids

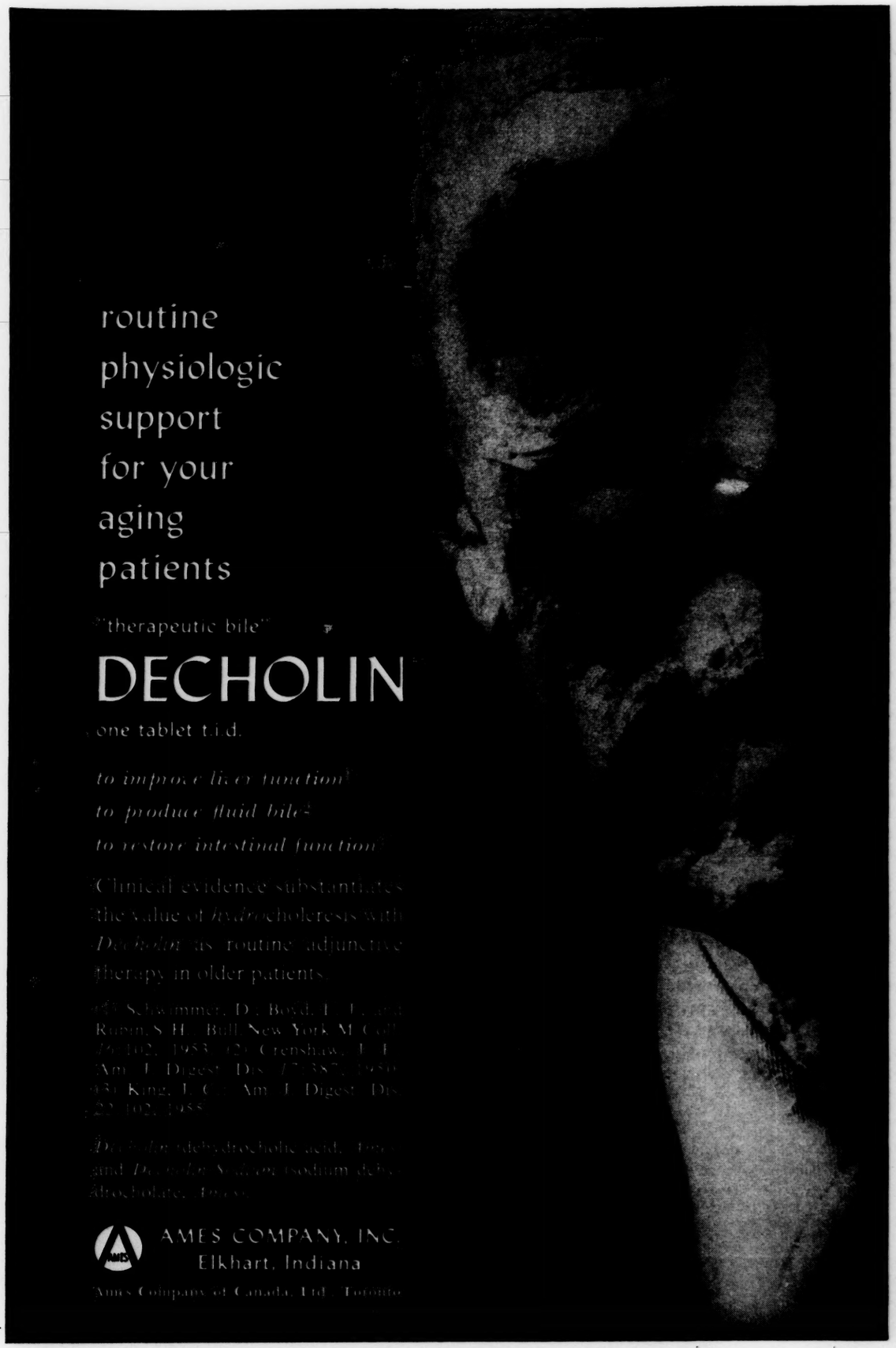
SQUIBB 200,000 UNIT BUFFERED PENICILLIN G POTASSIUM TABLETS

Recommended dosage: 1 or 2 tablets t.i.d. without regard to meals. Bottles of 12 and 100.

References: 1. Boger, W. P., J. Amer. Ger. Soc. 3:556, Aug. 1955. 2. Lapin, J. H., Ann. Allergy 13:169, March-April 1955. 3. Andelman, M. B. and Fischbein, W. I., Antibiotic Med. 1: 136, March 1955. 4. Statements of American Heart Association, Council on Rheumatic Fever and Congenital Heart Disease, Circulation 11:317, Feb. 1955. 5. Miller, J. M. et al., Antibiotics Annual 1954-55, Medical Encyclopedia Inc., N. Y., p. 105. 6. Seal, J. R. et al., J. Lab. & Clin. Med. 44:831, Dec. 1954. 7. Martin, W. J. et al., Am. Pract. & Dig. Treat. 5:813, Oct. 1954. 8. Henner, R., Eye, Ear, Nose & Throat Monthly 33:530, Sept. 1954. 9. Rodstein, M. and Young, D., Clin. Med. 61:695, Sept. 1954. 10. Bernstein, S. H. et al., A. M. A. Arch. Int. Med. 93:894, June 1954. 11. Craige, E., North Carolina M. J. 14:593, Dec. 1953. 12. Barach, A. L., J. Amer. Ger. Soc. 1:616, Sept. 1953. 13. Barach, A. L., Geriatrics 8:423, Aug. 1953. 14. Boger, W. P., Indus. Med. & Surg. 22:288, July 1953. 15. Young, D. and Rodstein, M., J.A.M.A. 152:987, July 1953. 16. Queries and Minor Notes, J.A.M.A. 152:1083, July 1953. 17. Roberts, E., A. M. A. Amer. J. Dis. Child. 85: 643, June 1953. 18. Spink, W. W., J.A.M.A. 152:585, June 1953. 19. Huang, N. N. and High, R. H., J. Pediat. 42:532, May 1953. 20. Antibiotics: Round Table Discussion, Pediatrics 11:270, March 1953. 21. Feinberg, B., Rhode Island M. J. 36: 138, March 1953. 22. Flippin, H. F., Delaware State M. J. 25: 55, March 1953. 23. Denny, F. W. Jr., Postgrad. Med. 13:153, Feb. 1953. 24. Flood, J. M., A. M. A. Arch. Dermat. & Syph. 67:42, Jan. 1953. 25. Kohn, K. H., Milzer, A. and MacLean, H., J.A.M.A. 151:347, Jan. 1953. 26. Siegal, S. et al., J. Allergy 24:1, Jan. 1953. 27. Statements of American Heart Association, Council on Rheumatic Fever and Congenital Heart Disease, J.A.M.A. 151:141, Jan. 1953. 28. Keefer, C. S., Pennsylvania M. J. 55:1177, Dec. 1952. 29. Kerrell, W. E., J.A.M.A. 150:1450, Dec. 1952. 30. Levy, D. F., Connecticut State M. J. 16:899, Dec. 1952. 31. Romansky, M. J. and Kelser, G. A., J.A.M.A. 150:1447, Dec. 1952. 32. Thomas L., Minnesota Med. 35:1105, Dec. 1952. 33. Jones, C. C., J. Iowa M. Soc. 42:533, Nov. 1952. 34. Reimann, H. A., Postgrad. Med. 12:255, Sept. 1952. 35. Bunn, P. A., N. Y. State J. Med. 52:2005, Aug. 1952. 36. Finland, M., New England J. Med. 247:557, Oct. 1952. 37. Babione, R. W. et al., U. S. Armed Forces M. J. 3:973, July 1952. 38. Hansen, A. E., South. M. J. 45:423, May 1952. 39. Dowling, H. F., G. P. 5:53, Feb. 1952. 40. Rhoades, P. S., G. P. 5:67, Feb. 1952. 41. Dowling, H. F. and Lepper, M. H., Med. Clin. North Amer., Jan. 1952, p. 247. 42. Karelitz, S. and Schifrin, N., Postgrad. Med. 11:17, Jan. 1952. 43. Panel Discussion, Pennsylvania M. J. 55:42, Jan. 1952. 44. Flippin, H. F. et al., J.A.M.A. 147:918, Nov. 1951. 45. Massell, B. F., Mod. Concepts Cardiovas. Dis. 20:105, Sept. 1951. 46. Weinstein, L., Boston Med. Quarterly 2:1, Sept. 1951. 47. Massell, B. F. et al., J.A.M.A. 146:1469, Aug. 1951. 48. Finland, M., Bull. New York Acad. Med., 27:199, April 1951. 49. Wheatley, D., Brit. M. J. 1:703, March 1951. 50. Keefer, C. S., Postgrad. Med. 9:101, Feb. 1951. 51. Bunn, P. A. et al., J.A.M.A. 144: 1540, Dec. 1950. 52. Weinstein, L. and Perrin, T. S., J. Pediat. 47:844, Dec. 1950. 53. Keefer, C. S., Am. J. Med. 7:216, Aug. 1949. 54. Robinson, J. A., Hirsch, H. L. and Dowling, H. F., Am. J. Med. 4:716, 1948. 55. Barach, A. L. and Garthwaite, B., Ann. Allergy 5:297, Aug. 1947. 56. Herrold, R. D., J. Urol. 57:897, May 1947. 57. White, H. J., Lee, M. E. and Alverson, C., Proc. Soc. Exper. Biol. & Med. 62:35, 1946. 58. Baumann, F. et al., J. Allergy 17:264, Sept. 1946. 59. Gamble, T. O. et al., Am. J. Obst. & Gynec. 50:514, Nov. 1945. 60. Woofter, A. C. and Hoffman, O. E., J. Iowa M. Soc. 35:189, May 1945.

'PENTIDS'® IS A SQUIBB TRADEMARK

SQUIBB Squibb Quality—the Priceless Ingredient



routine
physiologic
support
for your
aging
patients

"therapeutic bile"

DECHOLIN®

one tablet t.i.d.

to improve liver function[1]
to produce fluid bile[2]
to restore intestinal function[3]

[1] Clinical evidence substantiates the value of *hydro*choleresis with *Decholin* as "routine" adjunctive therapy in older patients.

[1] Schaumner, D.; Boyd, E. J. and Rubin, S. H.: Bull. New York M. Col. 26:102, 1953. [2] Grenshaw, L. E.: Am. J. Digest. Dis. 17:85, 1950. [3] King, L. C.: Am. J. Digest. Dis. 22:102, 1955.

Decholin—dehydrocholic acid, Ames and *Decholin Sodium*—sodium dehydrocholate, Ames.

AMES COMPANY, INC.
Elkhart, Indiana

Ames Company of Canada, Ltd., Toronto

Areas of Clinical Study / One of a Series

ANEMIA OF PREGNANCY

Maintenance of normal blood values during pregnancy is a factor in the welfare of the mother at delivery and in preventing anemia in the infant. Improvement in the patient's vitality and emotional stability during gestation can also be achieved.

RONCOVITE, *the original, clinically proved cobalt-iron product, has introduced a wholly new concept in the prevention and treatment of anemia. It is based on the unique hemopoietic stimulation produced only by cobalt. The application of this new concept routinely in pregnancy practically insures against the development of iron-deficiency; its use has also led to marked, dramatic advances in the successful treatment of many of the anemias.*

In a recent clinical study of anemia in pregnancy, Holly[1] *reports:*

—about 80 per cent of normal patients manifest significant decreases in hematologic values during pregnancy.

—conversely, 90 per cent of pregnant women maintained hemoglobin levels of 12 Gm. per cent or over when given Roncovite (iron-cobalt therapy). No other medication tested was so successful.

—in fact, 63 per cent of these Roncovite treated patients delivered with the unusually satisfactory level of 13 Gm. per cent hemoglobin.

—Roncovite (iron-cobalt therapy) has proven to be the most effective hematinic for maintaining an adequate hemoglobin level.

RONCOVITE IS A SAFE DRUG

In pregnancy—"No toxic manifestations associated with its use have been observed."[1]

In prematures—"None of them showed harmful effects despite the large doses..."[2]

In pharmacology—"Histopathologic studies of rats that received cobaltous chloride... revealed no significant degenerative changes in parenchymal organs as evidence of toxicity."[3]

SUPPLIED:

RONCOVITE TABLETS

Each enteric coated, red tablet contains:
Cobalt chloride..... 15 mg.
Ferrous sulfate exsiccated... 0.2 Gm.

RONCOVITE-OB

Each enteric coated, red capsule-shaped tablet contains:
Cobalt chloride..... 15 mg.
Ferrous sulfate exsiccated... 0.2 Gm.
Calcium lactate..... 0.9 Gm.
Vitamin D..... 250 units

RONCOVITE DROPS

Each 0.6 cc. (10 drops) provides:
Cobalt chloride
(Cobalt 9.9 mg.)..... 40 mg.
Ferrous sulfate.. ..... 75 mg.

DOSAGE:

One tablet after each meal and at bedtime. Children 1 year or over, 0.6 cc. (10 drops); infants less than 1 year, 0.3 cc. (5 drops) once daily diluted with water, milk, fruit or vegetable juice.

1. Holly, R. G.: Anemia in Pregnancy, Obstet. & Gynecol. *5*:562 (April) 1955.
2. Quilligan, J. J., Jr.: Texas State J. Med. *50:* 294 (May) 1954.
3. Hopps, H. C.; Stanley, A. J., and Shideler, A. M.: Polycythemia Induced by Cobalt, Amer. J. Clinical Path. *24:* (Dec.) 1954.

Bibliography of 192 references available on request.

RONCOVITE

The original, clinically proved cobalt-iron product

LLOYD BROTHERS, INC.
Cincinnati, Ohio

In the Service of Medicine Since 1870

Doctor, do you feel that your colleagues are missing important new medical findings by not reading The American Journal of Medicine?

Let us send them a complimentary copy—of course there is no obligation to you or your colleagues. Just fill out the coupon and mail it to us.

Dr. _____ *Dr.* _____

Address _____ *Address* _____

_____ _____

Dr. _____ *Your Name* _____

Address _____ *Address* _____

_____ _____

A.J.M.-6

The American Journal of Medicine

49 West 45th Street · New York 36, New York

new dosage form...

"MEDIATRIC" *Tablets*

For greater versatility of administration
in preventive geriatrics

Now you can prescribe "MEDIATRIC"...

TABLETS • CAPSULES • LIQUID

. . . to satisfy any individual preference among the steadily increasing number of aging patients you are treating with "Mediatric."

"MEDIATRIC"®

Steroid-Nutritional Compound

Tablets and Capsules

Each tablet or capsule contains:

Conjugated estrogens equine ("Premarin"®)	0.25 mg.
Methyltestosterone	2.5 mg.
Vitamin C (ascorbic acid)	50.0 mg.
Thiamine mononitrate (B_1)	5.0 mg.
Vitamin B_{12} with intrinsic factor concentrate	1/6 U.S.P. Unit
Folic acid U.S.P.	0.33 mg.
Ferrous sulfate exsic.	60.0 mg.
Brewers' yeast (specially processed)	200.0 mg.
d-Desoxyephedrine HCl	1.0 mg.

Supplied:

Tablets—No. 752—Bottles of 100 and 1,000.
Capsules—No. 252—Bottles of 30, 100, and 1,000.
Liquid—No. 910—Bottles of 16 fluidounces and 1 gallon.

Liquid

Each 15 cc. (3 teaspoonfuls) contains:

Conjugated estrogens equine ("Premarin"®)	0.25 mg
Methyltestosterone	2.5 mg.
Thiamine HCl (B_1)	5.0 mg.
Vitamin B_{12}	1.5 mcg.
Folic acid U.S.P.	0.33 mg.
d-Desoxyephedrine HCl	1.0 mg.

Contains 15% alcohol

Suggested Dosages:

Male—1 tablet or 1 capsule (or 3 teaspoonfuls) daily, or as required.

Female—1 tablet or 1 capsule (or 3 teaspoonfuls) daily, or as required, taken in 21 day courses with a rest period of one week between courses.

For continuing health and vigor in the "second 40 years"

Ayerst **Ayerst Laboratories • New York, N. Y. • Montreal, Canada**

5661

Advertisers Index

June, 1956

Abbott Laboratories 16, 24–25, 72
American Bakers Association 80
American Meat Institute 70
Ames Company, Inc. 4, 83
The Armour Laboratories 27, 71, 75
Ayerst Laboratories 71, 86
Burroughs Wellcome & Co., Inc. 48, 74, 75
Ciba Pharmaceutical Products, Inc. . . . . 14, 20–21, 54–55, 69, 76, *Back Cover*
Eaton Laboratories 26, 56
Endo Laboratories Inc. 81
The Glidden Company 73
Hoffmann-La Roche Inc. . . . . 18, *Insert Facing Page* 36, 47, 77
Irwin, Neisler & Company 52–53
International Minerals & Chemical Corporation 58–59
Lakeside Laboratories, Inc. 11
Lederle Laboratories 19, 30–31, 42, 60–61, 74
Thos. Leeming & Co., Inc. 30
Eli Lilly and Company 64
Lloyd Brothers, Inc. 84
The S. E. Massengill Company 15, 37, 62
McNeil Laboratories, Inc. 12–13
Organon Inc. 6
Parke, Davis & Company 33, 41, 49, 57
Pfizer Laboratories, Division, Chas. Pfizer & Co., Inc. 17, 29, 36, 44–45
Pharmacia Laboratories, Inc. 43
Riker Laboratories Inc. 34
A. H. Robins Co., Inc. 46
J. B. Roerig Co. 22–23
Schieffelin & Co. 68
G. D. Searle & Co. 65
Sharp & Dohme 10, 50–51, 63
Sherman Laboratories 40
E. R. Squibb & Sons, Division of Mathieson Chemical Corp. 8, 28, 39, 66–67, 82
The Upjohn Company 35
Varick Pharmacal Company, Inc. 38
Walker Laboratories, Inc. 78
Wallace Laboratories 32
Warner-Chilcott Laboratories 1
Winthrop Laboratories 2

STABILIZE

the up and down patient

Serpasil
tranquilizer

Ritalin
psychomotor stimulant

Serpatilin
emotional stabilizer

To induce emotional equilibrium in those who swing from anxiety to depression, Serpatilin combines the relaxing, tranquilizing action of Serpasil with the mild mood-lifting effect of the new cortical stimulant, Ritalin. In recent months, numerous clinical studies have indicated the value of combining these agents for the treatment of various disorders marked by tension, nervousness, anxiety, apathy, irritability and depression. Arnoff,[1] in a study of 51 patients, found the combination of definite value in a variety of complaints, noting no effect on blood pressure or heart rate. Lazarte and Petersen[2] also found Serpatilin effective in counteracting the side effects of reserpine and chlorpromazine. They reported: "The stimulating effect of Ritalin seemed complementary to the action of reserpine . . . in that it brought forth a better quality of increased psychomotor activity."

1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M.C.: Personal communication.

Serpatilin Tablets, 0.1 mg./10 mg., each containing 0.1 mg. Serpasil® (reserpine CIBA) and 10 mg. Ritalin® hydrochloride (methyl-phenidylacetate hydrochloride CIBA).

Dosage: 1 tablet b.i.d. or t.i.d., adjusted to the individual.

CIBA
SUMMIT, N. J.

Serpatilin T.M.

(reserpine and methyl-phenidylacetate hydrochloride CIBA)

2/22004M